CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074023

Trade Name: RANITIDINE TABLETS USP 150MG AND 300MG (PRESENT AS THE HYDROCHLORIDE)

Generic Name: Ranitidine Tablets USP 150mg and 300mg (Present as the hydrochloride)

Sponsor : Lipha Pharmaceuticals, Inc.

Approval Date: August 22, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074023

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074023

APPROVAL LETTER

ANDA 74-023

AUG 2 2 1997

Lipha Pharmaceuticals, Inc.
U.S. Agent for: Genpharm Inc.
Attention: Anita M. Goodman, M.D.
9 West 57th Street, Suite 3825
New York, NY 10019

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated February 4, 1991, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Ranitidine Tablets USP, 150 mg and 300 mg (present as the hydrochloride).

Reference is also made to your correspondence dated June 16, and July 31, 1997, and to your amendments dated July 8, 1997, and August 18, 1997.

The listed drug product referenced in your application is subject to a period of patent protection which expires on June 4, 2002, (patent 4,521,431). Your ANDA for ranitidine hydrochloride initially contained paragraph IV certifications to both the '658 patent (expired on July 25, 1997) and the '431 patent. The resulting lawsuits, Glaxo Inc. and Glaxo Group Limited, v. Genpharm Pharmaceuticals, Inc., Civil Action No. 91-222CIV5-BO in the U.S. District Court for the Eastern District of North Carolina (Raleigh Division) and Allen & Hanburys Limited v. Genpharm Pharmaceuticals, Inc., Civil Action No. K-93-4228 in the U.S. District Court for the District of Maryland, ended in a Final Judgment on Consent, finding the listed patents valid, enforceable, and infringed. You subsequently amended your ANDA and submitted a paragraph III certification to the '658 patent and a paragraph IV certification to the '431 patent. On August 18, 1997 you notified OGD that an Order dismissing with prejudice the claims of plaintiff Glaxo in Glaxo Wellcome Inc., et al, v. Genpharm Inc., Civil Action No. 96 CIV-6719(DAB) was rendered on August 15, 1997 in the U.S. District Court for the Southern District of New York.

The Agency has reviewed the application for issues related to the 180-day exclusivity provisions under section 505(j)(4)(B)(iv) of the Act to ANDAs submitted for ranitidine hydrochloride tablets. As explained in earlier correspondence, the Agency has concluded that Genpharm, Inc., as the first ANDA applicant with a paragraph IV certification to the patent listed for the reference drug,

receives 180-days of exclusivity. The Agency has concluded that Genpharm, Inc.'s 180-day period of exclusivity began on March 3, 1997, and will expire on August 29, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Ranitidine Tablets USP, 150 mg and 300 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Zantac Tablets, 150 mg and 300 mg, respectively, of Glaxo Wellcome, Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

[redacted]

for

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

8-22-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074023

FINAL PRINTED LABELING

Each tablet contains ranitidine hydrochloride equivalent to 150 mg ranitidine.

USUAL DOSAGE: See package insert for Dosage and Administration.

Store at controlled room temperature 15° to 30°C (59° to 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

Dispense in a tight, light-resistant container as defined in the USP.

001-123 REV.# 00

NDC 55567-0030-5 1000 TABLETS

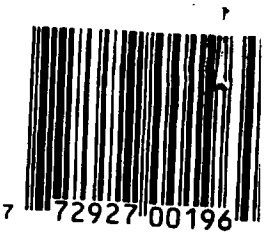
RANITIDINE

TABLETS USP

150 mg

CAUTION: Federal law prohibits dispensing without prescription

Manufactured by:
GENPHARM INC.
Toronto, Canada
M8Z 2S6
1-800-661-7134



Each tablet contains ranitidine hydrochloride equivalent to 300 mg ranitidine.

Usual Adult Dosage: One tablet daily at bedtime or as directed by physician.

See package insert for full prescribing information.

Store at controlled room temperature 15° to 30°C (59° to 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

Dispense in a tight, light-resistant container as defined in the USP.

001-124 REV.# 00

NDC 55567-0031-5 1000 TABLETS

RANITIDINE

TABLETS USP

[redacted]

CAUTION: Federal law prohibits dispensing without prescription

Manufactured by:
GENPHARM INC.
Toronto, Canada
M8Z 2S6
1-800-661-7134

Each tablet contains ranitidine hydrochloride equivalent to 150 mg ranitidine.

USUAL DOSAGE: See package insert for Dosage and Administration.

Store at controlled room temperature 15° to 30°C (59° to 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

Dispense in a tight, light-resistant container as defined in the USP.

001-121 REV.#00

NDC 55567-0030-7 60 TABLETS

RANITIDINE

TABLETS USP

150 mg

CAUTION: Federal law prohibits dispensing without prescription

Manufactured by:
GENPHARM INC.
Toronto, Canada
M8Z 2S6
1-800-661-7134

7 72927 00195 7

Each tablet contains ranitidine hydrochloride equivalent to 300 mg ranitidine.

Usual Adult Dosage: One tablet daily at bedtime or as directed by a physician.

See package insert for full prescribing information

Store at controlled room temperature 15° to 30°C (59° to 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

Dispense in a tight, light-resistant container as defined in the USP.

001-122 REV.# 00

NDC 55567-0031-6 30 TABLETS

RANITIDINE

TABLETS USP

[redacted]

CAUTION: Federal law prohibits dispensing without prescription

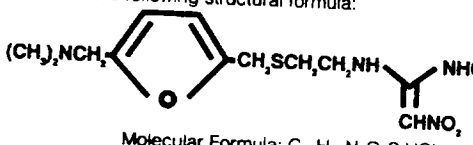
Manufactured by:
GENPHARM INC.
Toronto, Canada
M8Z 2S6
1-800-661-7134

7 72927 00198 8

RANITIDINE TABLETS USP

DESCRIPTION

Ranitidine hydrochloride is a histamine H_2-receptor antagonist. Chemically it is *N*-[2-[[[5-[(Dimethylamino)methyl]-2-furanyl] methyl]thio]ethyl]-*N'*-methyl-2-nitro-1,1-ethenediamine, hydrochloride. Ranitidine hydrochloride is a white to pale yellow, crystalline powder that is very soluble in water. It has a slightly bitter taste and sulfur-like odor. It has the following structural formula:



Molecular Formula: $C_{13}H_{22}N_4O_3S.HCl$
Molecular Weight: 350.87

Each tablet, for oral administration, contains 168 mg or 336 mg of ranitidine equivalent to 150 mg or 300 mg of ranitidine respectively. In addition, each tablet contains the following inactive ingredients: hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, titanium dioxide and triethyl citrate. Each 300 mg tablet also contains croscarmellose sodium.

CLINICAL PHARMACOLOGY

Ranitidine is a competitive, reversible inhibitor of the action of histamine at the histamine H_2-receptors, including receptors on the gastric cells. Ranitidine does not lower serum Ca^{++} in hypercalcemic states. Ranitidine is not an anticholinergic agent.

Antisecretory Activity:

1. Effects on Acid Secretion: Ranitidine inhibits both daytime and nocturnal basal gastric acid secretions as well as gastric acid secretion stimulated by food, betazole, and pentagastrin, as shown in the following table:

Effect of Oral Ranitidine on Gastric Acid Secretion

	Time after Dose, h	% Inhibition of Gastric Acid Output by Dose, mg			
		75-80	100	150	200
Basal	Up to 4		99	95	
Nocturnal	Up to 13	95	96	92	
Betazole	Up to 3		97	99	
Pentagastrin	Up to 5	58	72	72	80
Meal	Up to 3		73	79	95

It appears that basal-, nocturnal-, and betazole-stimulated secretions are most sensitive to inhibition by ranitidine, responding almost completely to doses of 100 mg or less, while pentagastrin- and food-stimulated secretions are more difficult to suppress.

2. Effects on Other Gastrointestinal Secretions:

Pepsin: Oral ranitidine does not affect pepsin secretion. Total pepsin output is reduced in proportion to the decrease in volume of gastric juice.

Intrinsic Factor: Oral ranitidine had no significant effect on pentagastrin-stimulated intrinsic-factor secretion.

Serum Gastrin: Ranitidine has little or no effect on fasting or postprandial serum gastrin.

Other Pharmacologic Actions:

a. Gastric bacterial flora — increase in nitrate-reducing organisms, significance not known.

b. Prolactin levels — no effect in recommended oral or IV dosage, but small, transient, dose-related increases in serum prolactin have been reported after IV bolus injections of 100 mg or more.

c. Other pituitary hormones — no effect on serum gonadotropins, TSH, or GH. Possible impairment of vasopressin release.

d. No change in cortisol, aldosterone, androgen, or estrogen levels.

e. No antiandrogenic action.

f. No effect on count, motility, or morphology of sperm.

Pharmacokinetics: Ranitidine is 50% absorbed after oral administration, compared

In these studies patients treated with ranitidine reported a reduction in both daytime and nocturnal pain, and they also consumed less antacid than the placebo-treated patients.

Mean Daily Doses of Antacid

	Ulcer Healed	Ulcer Not Healed
Ranitidine	0.06	0.71
Placebo	0.71	1.43

Foreign studies have shown that patients heal equally well with 150 mg b.i.d. and 300 mg hs (85% versus 84%, respectively) during a usual 4-week course of therapy. If patients require extended therapy of 8 weeks, the healing rate may be higher for 150 mg b.i.d. as compared to 300 mg hs (92% versus 87%, respectively).

Studies have been limited to short-term treatment of acute duodenal ulcer. Patients whose ulcers healed during therapy had recurrences of ulcers at the usual rates.

Maintenance Therapy in Duodenal Ulcer: Ranitidine has been found to be effective as maintenance therapy for patients following healing of acute duodenal ulcers. In two independent, double-blind, multicenter, controlled trials, the number of duodenal ulcers observed was significantly less in patients treated with ranitidine (150 mg hs) than in patients treated with placebo over a 12-month period.

Duodenal Ulcer Prevalence

Double-Blind, Multicenter, Placebo-Controlled Trials					
Multicenter Trial	Drug	Duodenal Ulcer Prevalence			No. of Patients
		0 - 4 Months	0 - 8 Months	0 - 12 Months	
USA	RAN	20%*	24%*	35%*	138
	PLC	44%	54%	59%	139
Foreign	RAN	12%*	21%*	28%*	174
	PLC	56%	64%	68%	165

% = Life-Table estimate
* = $p<0.05$ (ranitidine versus comparator)
RAN = ranitidine
PLC = Placebo

As with other H_2-antagonists, the factors responsible for the significant reduction in the prevalence of duodenal ulcers include prevention of recurrence of ulcers, more rapid healing of ulcers that may occur during maintenance therapy, or both.

Gastric Ulcer: In a multicenter, double-blind, controlled, US study of endoscopically diagnosed gastric ulcers, earlier healing was seen in the patients treated with ranitidine as shown in the following table:

	Ranitidine*		Placebo*	
	Number Entered	Healed/ Evaluable	Number Entered	Healed/ Evaluable
Outpatients				
Week 2	92	16/83 (19%)	94	10/83 (12%)
Week 6		50/73 (68%)		35/69 (51%)

more.

c. Other pituitary hormones — no effect on serum gonadotropins, TSH, or GH. Possible impairment of vasopressin release.

d. No change in cortisol, aldosterone, androgen, or estrogen levels.

e. No antiandrogenic action.

f. No effect on count, motility, or morphology of sperm.

Pharmacokinetics: Ranitidine is 50% absorbed after oral administration, compared to an IV injection with mean peak levels of 440 to 545 ng/mL occurring at 2 to 3 hours after a 150 mg dose. The elimination half-life is 2.5 to 3 hours.

Absorption is not significantly impaired by the administration of food or antacids. Propantheline slightly delays and increases peak blood levels of ranitidine, probably by delaying gastric emptying and transit time. In one study, simultaneous administration of high-potency antacid (150 mmol) in fasting subjects has been reported to decrease the absorption of ranitidine.

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36 to 94 ng/mL. Following a single oral dose of 150 mg, serum concentrations of ranitidine are in this range up to 12 hours. However, blood levels bear no consistent relationship to dose or degree of acid inhibition.

The principal route of excretion is the urine, with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 410 mL/min, indicating active tubular excretion. Four patients with clinically significant renal function impairment (creatinine clearance 25 to 35 mL/min) administered 50 mg of ranitidine intravenously had an average plasma half-life of 4.8 hours, a ranitidine clearance of 29 mL/min, and a volume of distribution of 1.76 L/kg. In general, these parameters appear to be altered in proportion to creatinine clearance (see DOSAGE AND ADMINISTRATION).

In man, the N-oxide is the principal metabolite in the urine; however, this amounts to less than 4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl ranitidine (1%). The remainder of the administered dose is found in the stool. Studies in patients with hepatic dysfunction (compensated cirrhosis) indicate that there are minor, but clinically insignificant, alterations in ranitidine half-life, distribution, clearance, and bioavailability.

The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

Clinical Trials: Active Duodenal Ulcer: In a multicenter, double-blind, controlled US study of endoscopically diagnosed duodenal ulcers, earlier healing was seen in the patients treated with ranitidine as shown in the following table:

	Ranitidine*		Placebo*	
	Number Entered	Healed/ Evaluable	Number Entered	Healed/ Evaluable
Outpatients				
Week 2	195	69/182 (38%)†	188	31/164 (19%)
Week 4		137/187 (73%)†		76/168 (45%)

*All patients were permitted p.r.n. antacids for relief of pain.
†$p<0.0001$

the following table:

	Ranitidine*		Placebo*	
	Number Entered	Healed/ Evaluable	Number Entered	Healed/ Evaluable
Outpatients				
Week 2	92	16/83 (19%)	94	10/83 (12%)
Week 6		50/73 (68%)†		35/69 (51%)

*All patients were permitted p.r.n. antacids for relief of pain.
†$p=0.009$

In this multicenter trial, significantly more patients treated with ranitidine became pain-free during therapy.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): Ranitidine inhibits gastric acid secretion and reduces occurrence of diarrhea, anorexia, and pain in patients with pathological hypersecretion associated with Zollinger-Ellison syndrome, systemic mastocytosis, and other pathological hypersecretory conditions (e.g., postoperative, "short-gut" syndrome, idiopathic). Use of ranitidine was followed by healing of ulcers in 8 of 19 (42%) patients who were intractable to previous therapy.

Gastroesophageal Reflux Disease (GERD): In two multicenter, double-blind, placebo-controlled, 6-week trials performed in the United States and Europe, ranitidine 150 mg b.i.d. was more effective than placebo for the relief of heartburn and other symptoms associated with GERD. Ranitidine-treated patients consumed significantly less antacid than did placebo-treated patients.

The US trial indicated that ranitidine 150 mg b.i.d. significantly reduced the frequency of heartburn attacks and severity of heartburn pain within one to two weeks after starting therapy. The improvement was maintained throughout the 6-week trial period. Moreover, patient response rates demonstrated that the effect on heartburn extends through both the day and night time periods.

In two additional U.S. multicenter, double-blind, placebo-controlled, 2-week trials, ranitidine 150 mg b.i.d. was shown to provide relief of heartburn pain within 24 hours of initiating therapy and a reduction in the frequency and severity of heartburn.

Erosive Esophagitis: In two multicenter, double-blind, randomized, placebo-controlled, 12-week trials performed in the United States, ranitidine 150 mg q.i.d. was significantly more effective than placebo in healing endoscopically diagnosed erosive esophagitis and in relieving associated heartburn. The erosive esophagitis healing rates were as follows:

Erosive Esophagitis Patient Healing Rates

	Healed/Evaluable	
	Placebo* n=229	Ranitidine 150 mg q.i.d.* n=215
Week 4	43/198 (22%)	96/206 (47%)†
Week 8	63/176 (36%)	142/200 (71%)†
Week 12	92/159 (58%)	162/192 (84%)†

* All patients were permitted p.r.n. antacids for relief of pain.
†$p<0.001$ versus placebo.

No additional benefit in healing of esophagitis or in relief of heartburn was seen with a ranitidine dose of 300 mg q.i.d.

INDICATIONS AND USAGE

Ranitidine tablets are indicated in:

1. Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks. Studies available to date have not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than eight weeks.
2. Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers. No placebo-controlled comparative studies have been carried out for periods of longer than 1 year.
3. The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of active, benign gastric ulcer. Most patients heal within 6 weeks and the usefulness of further treatment has not been demonstrated. Studies available to date have not assessed the safety of ranitidine in uncomplicated, benign gastric ulcer for periods of more than 6 weeks.
5. Treatment of GERD: Symptomatic relief commonly occurs within 24 hours after starting therapy with ranitidine 150 mg b.i.d.
6. Treatment of endoscopically-diagnosed erosive esophagitis. Symptomatic relief of heartburn commonly occurs within 24 hours of therapy initiation with ranitidine 150 mg q.i.d.

Concomitant antacids should be given as needed for pain relief to patients with active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; GERD; and erosive esophagitis.

CONTRAINDICATIONS

Ranitidine tablets are contraindicated in patients known to have hypersensitivity to the drug or any of the ingredients (see PRECAUTIONS).

PRECAUTIONS

General: 1. Symptomatic response to ranitidine therapy does not preclude the presence of gastric malignancy.
2. Since ranitidine is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ranitidine is metabolized in the liver.
3. Rare reports suggest that ranitidine may precipitate acute porphyric attacks in patients with acute porphyria. Ranitidine should therefore, be avoided in patients with a history of acute porphyria.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ranitidine therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ranitidine has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ranitidine may affect the bioavailability of certain drugs by some mechanism as yet unidentified (e.g., a pH-dependent effect on absorption or a change in volume of distribution).

Increased or decreased prothrombin times have been reported during concurrent use of ranitidine and warfarin. However, in human pharmacokinetic studies with dosages of ranitidine up to 400 mg per day, no interaction occurred; ranitidine had no effect on warfarin clearance or prothrombin time. The possibility of an interaction with warfarin at dosages of ranitidine higher than 400 mg per day has not been investigated.

...mg q.i.d. intravenously for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. intravenously for 5 days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

Musculoskeletal: Rare reports of arthralgias and myalgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ranitidine and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ranitidine has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ranitidine, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases of erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE

There has been limited experience with overdosage. Reported acute ingestions of up to 18 g orally have been associated with transient adverse effects similar to those encountered in normal clinical experience (see ADVERSE REACTIONS). In addition, abnormalities of gait and hypotension have been reported.

When overdosage occurs, the usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring, and supportive therapy should be employed.

Studies in dogs receiving dosages of ranitidine in excess of 225 mg/kg per day have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1,000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in mice and rats were 77 and 83 mg/kg, respectively.

DOSAGE AND ADMINISTRATION

Active Duodenal Ulcer: The current recommended adult oral dosage of ranitidine for duodenal ulcer is 150 mg twice daily. An alternative dosage of 300 mg once daily after the evening meal or at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated (see CLINICAL PHARMACOLOGY, Clinical Trials: *Active Duodenal Ulcer*). Smaller doses have been shown to be equally effective in inhibiting gastric acid secretion in US studies, and several foreign trials have shown that 100 mg b.i.d. is as effective as the 150 mg dose.

Antacid should be given as needed for relief of pain (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Maintenance of Healing of Duodenal Ulcers: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): Th...

ranitidine and warfarin. However, in human pharmacokinetic studies with dosages of ranitidine up to 400 mg per day, no interaction occurred; ranitidine had no effect on warfarin clearance or prothrombin time. The possibility of an interaction with warfarin at dosages of ranitidine higher than 400 mg per day has not been investigated.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg per day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ranitidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Ranitidine is secreted in human milk. Caution should be exercised when ranitidine is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age-groups.

ADVERSE REACTIONS

The following have been reported as events in clinical trials or in the routine management of patients treated with ranitidine . The relationship to ranitidine therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ranitidine administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported. Rare reports of reversible involuntary motor disturbances have been received.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving

pa[illegible] (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Maintenance of Healing of Duodenal Ulcers: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ranitidine 150 mg doses more frequently. Dosages should be adjusted to individual patient needs, and should continue as long as clinically indicated. Dosages up to 6 g per day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Erosive Esophagitis: The current recommended adult oral dosage is 150 mg four times a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ranitidine, the recommended dosage in patients with a creatinine clearance less than 50 mL/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED

Ranitidine Tablets USP, 150 mg and 300 mg for oral administration are available as:

150 mg tablets -

White to off-white, round, film-coated, unscored tablets with "G" on one side and "00" over "30" on the other.

Bottles of 60 - NDC # 55567-0030-7
Bottles of 1000 - NDC # 55567-0030-5

300 mg tablets -

White to off-white, capsule shaped, film-coated, unscored tablets with "G" on one side and "0031" on the other.

Bottles of 30 - NDC # 55567-0031-6
Bottles of 1000 - NDC # 55567-0031-5

Store at controlled room temperature between 15° and 30°C (59° and 86°F) in a dry place.

Protect from light.

Replace cap securely after each opening. Dispense in a tight, light-resistant container as defined in the USP.

CAUTION: Federal Law prohibits dispensing without prescription.

Manufactured by:
GENPHARM INC.
Toronto, Canada
M8Z 2S6
1-800-661-7134

002-176 REV.#03 dated March 25, 1997.

4

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074023

CHEMISTRY REVIEW(S)

1. SECOND ADDENDUM TO CHEMIST'S REVIEW NO. 6

2. ANDA # 74-023

3. NAME AND ADDRESS OF APPLICANT
Genpharm Pharmaceuticals Inc.
37 Advanced Road
Etobicoke
Ontario, Canada, M8Z 2S6

4. LEGAL BASIS for ANDA SUBMISSION
Patent #4,128,658 which covers Polymorphic Form I expired on July 25, 1997.

5. SUPPLEMENT
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Ranitidine Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

February 4, 1991--	Original Submission
February 14, 1991-	Original New Correspondence
February 18, 1991-	Original New Correspondence
March 15, 1991--	Acceptable for filing on 2/15/91
March 29, 1991--	New Correspondence
August 15, 1991--	Professional Labeling Review
February 5, 1992--	Bio Review--Unacceptable
March 23, 1992--	Chemistry Review by M. Theodorakis
May 1, 1992--	Deficiency letter
November 18, 1992-	New Correspondence--Bio
April 20, 1993--	Bio Review
May 28, 1993--	Bio deficiency letter
September 13, 1993-	Bio deficiency letter
November 12, 1993--	New Correspondence-P IV
November 30, 1994-	Amendment (First)
November 30, 1994--	Bio Review--Satis
December 14, 1994--	New Correspondence
July 3, 1995--	Amendment (Second)
December 16, 1995--	Deficiency letter
May 6, 1996--	Amendment (Third) including additional information (new source of nds)
August 26, 1996--	Deficiency letter
September 27, 1996--	Amendment (Fourth)
December 16, 1996--	Unsolicited amendment
March 3, 1997--	New Correspondence
March 21, 1997--	Deficiency letter
April 2, 1997--	Facsimile Amendment
April 17, 1997--	Labeling review--acceptable
April 17 & 18, 1997-	New correspondences
April 30, 1997--	Chemistry review no. 6--no chemistry

	issues pending
May 12, 1997--	Bio review (Form I)--acceptable
May 16, 1997--	Bio letter
June 16, 1997--	New correspondence reflecting exclusivity statement
June 17, 1997--	TA letter
July 8, 1997--	Amendment--No changes made to the application since TA was granted
July 15, 1997--	Letter updating applicant on litigation status
July 25, 1997--	Information letter to applicant
July 31, 1997--	New correspondence--applicant waives exclusivity to Granutec
August 18, 1997--	Amendment--Change in status from P IV to P III

10. PHARMACOLOGICAL CATEGORY
H2 Receptor Antagonist

11. Rx or OTC
Rx

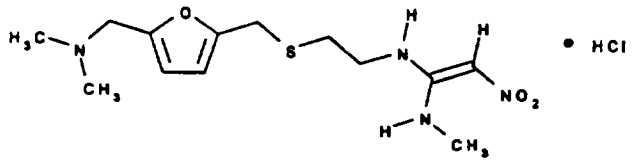
12. RELATED DMFs

[redacted]

13. DOSAGE FORM
Coated Tablets

14. POTENCY
150 mg & 300 mg

15. CHEMICAL NAME AND STRUCTURE
Ranitidine Hydrochloride USP
$C_{13}H_{22}N_4O_3S.HCl$; M.W. = 350.87



N-[2-[[[5-[(Dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, hydrochloride.
CAS [66357-59-3]

16. RECORDS AND REPORTS
None

17. COMMENTS
The minor amendment submitted on July 8, 1997, indicates that no changes have been made to the application since the

date of its tentative approval. On July 31, 1997, the applicant waived its exclusivity to which it was entitled to Granutec. On August 18, 1997, we were informed of an Order dismissing with prejudice the claims of plaintiff Glaxo versus the applicant.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval letter to issue.

19. REVIEWER:
Edwin Ramos

[redacted]

DATE COMPLETED:
August 22, 1997

8/21/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074023

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA: #74-023 **SPONSOR:** Genpharm Inc.
DRUG: Ranitidine HCl
DOSAGE FORM: Tablets
STRENGTH: 150 mg
TYPE OF STUDY: Dissolution Testing, Waiver Request

DISSOLUTION TESTING SUMMARY:

The dissolution testing conducted on 12 units of each test and reference product are acceptable. Not Less Than [redacted](Q) of the labeled amount was dissolved in 45 minutes.

WAIVER OF BIOEQUIVALENCE STUDY:

The waiver of bioequivalence study requirements for 150 mg Ranitidine Tablets, USP may be granted according to 21 CFR, 320.22 (d)(2) based on the following:

(a) Acceptable single-dose bioequivalence study conducted under fasting conditions on the higher strength of Ranitidine Tablets, USP, 300 mg, and Zantac Tablets, 300 mg.

(b) Acceptable dissolution testing conducted on Ranitidine Tablets, 300 and 150 mg, and Zantac Tablets, 300 and 150 mg.

(c) The similarity between the formulations of Ranitidine Tablets, USP, 300 and 150 mg.

PRIMARY REVIEWER: F. Nouravarsani **BRANCH:** III

SIGNITURE: [redacted] **DATE:** August 04, 1995

BRANCH CHIEF: R. Mhatre **BRANCH:** III

SIGNITURE: [redacted] for **DATE:** 8/14/95

DIRECTOR: K. Chan
DIVISION OF BIOEQUIVALENCE:

SIGNITURE: [redacted] **DATE:** 8/9/95

DIRECTOR:
OFFICE OF GENERIC DRUGS:

SIGNITURE: [redacted] **DATE:** 8/16/95

AUG 1 1995

Ranitidine Tablets, USP
300 mg, and 150 mg
ANDA #74-023
Reviewer: F. Nouravarsani
74023SDW.N94

Genpharm Inc.
Ontario, Canada
Submission Date:
November 30, 1994

Review of a Bioequivalence Study, Dissolution Testing, and Waiver Request

INTRODUCTION:

Genpharm Inc. has submitted a single dose bioequivalence study conducted under fasting conditions on its test product, Ranitidine Tablets, USP, 300 mg and the listed reference product, Zantac Tablets, 300 mg (NDA #18703-002, December 09, 1985) manufactured by Glaxo (USA).

The firm has also submitted comparative dissolution testing conducted on Ranitidine Tablets and Zantac Tablets, 300 and 150 mg, and has requested for waiver of the bioequivalence study requirements for 150 mg Ranitidine Tablets.

Ranitidine hydrochloride, a histamine H2-receptor antagonist inhibits daytime and nocturnal basal gastric acid secretions. It also inhibits the gastric acid secretion stimulated by meal, pentagastrin, and betazole. The oral absolute bioavailability of Zantac is 50%. Mean peak levels of ranitidine are 440 to 545 ng/mL observed at 2 to 3 hours following a 150 mg dose. The elimination half-life is reported to be 2.5 to 3 hours.

The administration of food or antacids does not show a significant effect on the absorption of Zantac.

OBJECTIVES:

1. Determine single dose bioequivalency of the test product, Ranitidine Tablets, USP, 300 mg, and the reference product, Zantac Tablets, 300 mg under fasting conditions.

2. Compare dissolution testing conducted on the test and reference products, Ranitidine and Zantac Tablets, 300 and 150 mg.

3. Waiver request of bioequivalence study requirements for the Ranitidine Tablets, 150 mg.

BIOEQUIVALENCE STUDY:

Sponsor: Genpharm Inc. Pharmaceuticals, Etobicoke, Ontario, Canada.
Manufacturer: Genpharm Inc. Pharmaceuticals.

[redacted]

[redacted]

Study Design:

A randomized, single dose, open-label, two - way crossover study design (Protocol #10532B/Study #106-18-10532-94).

Treatments:

Treatment A (test Product): A single dose of Ranitidine Tablets, 300 mg, lot #100316 (expiration date: not available). Batch size [redacted] Tablets.

Treatment B (reference Product): A single dose of Zantac Tablets, 300 mg, lot #Z11583KP, expiration date: September 1995.

Clinical Study Date:

Phase I: August 18-20, 1994
Phase II: August 25-27, 1994
Washout period: one week.

Subjects:

Twenty-six (26) healthy male volunteers participated and completed the study. Subjects #1, 4, 6, 7, 10, 12, 14, 16, 17, 19, 21, 24 and 25 received treatment A in period I. The rest of the subjects (#2, 3, 5, 8, 9, 11, 13, 15, 18, 20, 22, 23, and 26) received treatment A in period II.

The range of subject's age, weight, and height are summarized as follows:

Age: 18 - 44 years
Weight: 130 - 205 pounds
Height: 64 - 75 inches

Housing, Fasting, Food and Fluid Intake:

All subjects were housed from approximately 12 hours before the dose administration until 24 hour postdose during each phase. They fasted overnight, for not less than 10 hours prior to the dosing and 5 hours after the dose. The dose was taken with 240 mL of water. The same meals were served throughout each phase. The subjects were not allowed to smoke from 1 hour before the dose until 4 hours postdose.

Blood Samples:

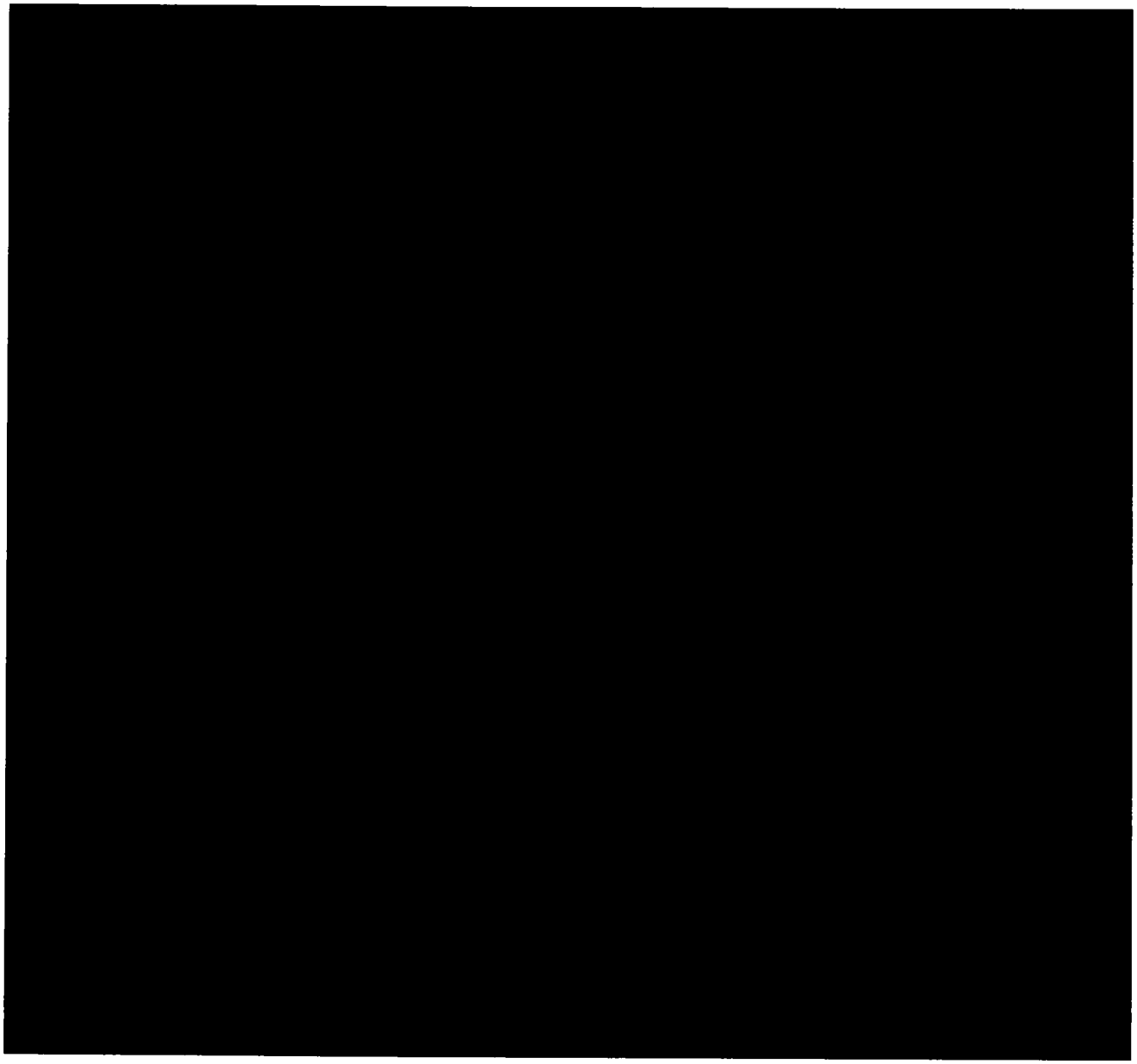
Blood samples (10 mL each) were collected in Vacutainers with no anticoagulant at predose, and at 0.33, 0.67, 1.00 1.33 1.67, 2.00,

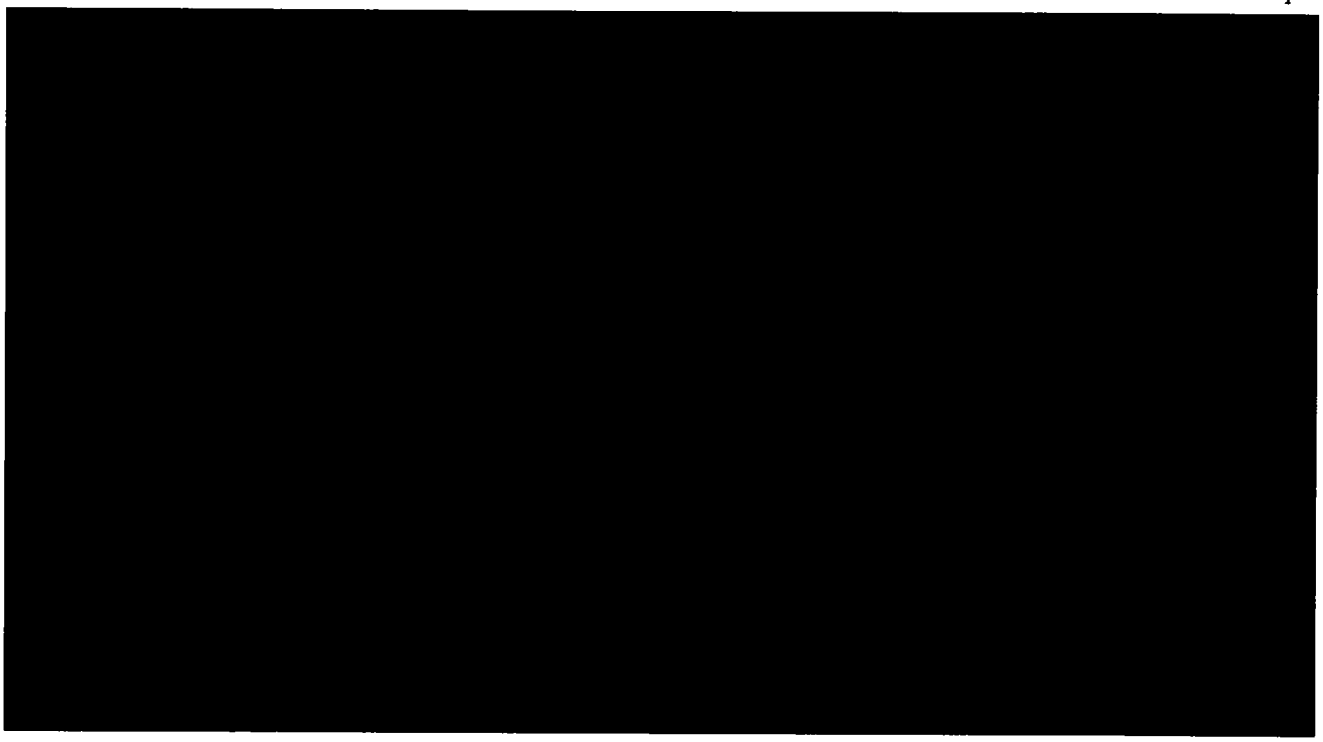
2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.0, 16.0, and 20.00 hours. The samples were allowed to clot by keeping them at room temperature for 30 minutes, and then were centrifuged at 10° C. The serum samples were stored at -20° C.

Safety Monitoring:

Seated blood pressure and pulse rate were determined at predose, and at 4, and 24 hours following the administration of the dose. Temperature and respirations were measured at predose and 24 hours postdose.

Analytical Procedures:





Statistical Analysis:

The data were analyzed using SAS - GLM procedure. The two one sided t-test procedure (90% confidence intervals) was used to compare the Ln-transformed and Un-transformed least squares mean parameters of AUC(0-T), AUC(0-Inf), and C(Max) obtained from the test and reference products.

Results:

The mean serum ranitidine concentrations are summarized in Table 1. There are no statistically significant differences between the mean concentrations at each sampling time (p=0.05) for the test and reference products except for samples at 10 and 12 hours.

Linear Plot of the mean serum concentrations of ranitidine versus time for both test and reference products are shown in Figure 1.

The pharmacokinetic parameters are compared in Table 2. There were no statistically significant differences between the test and reference products' parameters (p=0.05).

The AUC(0-T) for the test product, 4855 hr*ng/mL, is comparable with the AUC(0-T) of 5021 hr*ng/mL for the reference product.

The AUC(0-Inf) for the test product, 4932 hr*ng/mL, is comparable with the one obtained for the reference product, 5094 hr*ng/mL.

The C(Max) for the test product, 1090 ng/mL, is comparable with the

C(Max) of 1075 ng/mL for the reference product.

[redacted]

Mean AUC(0-T)/AUC(0-Inf) ratios for the test and reference products were 98.4% and 98.6%, respectively (Table 3).

Mean test/reference ratios for AUC(0-T), AUC(0-Inf), and C(Max), were 99.7%, 99.7% and 106.9%, respectively (Table 4).

The 90% confidence intervals for AUC(0-T), AUC(0-Inf), and C(Max) based on least squares means are summarized in Table 2. There are no product and period effects (p=0.05) observed for the above parametetrs using Ln-transformed or un-transformed data. There is sequence effect (p=0.1) for AUC(0-T): [p=0.0388]; Ln AUC(0-T): [p=0.0574]; AUC(0-Inf): [p=0.0419]; LnAUC(0-Inf): [p=0.0606]; C(Max): [p=0.0515]; and LnC(Max): [p=0.0732].

Adverse Experiences:

Four subjects complained about the following adverse experiences:

Complaint	Subject No.	Treatment	Relation to Drug
Sore throat (mild)	7	A	None
Right eye irritation (mild)	12	B	None
Muscle Pain left upper chest (mild)	14	A	None
Flushed feeling, warm sensation mid sternum (mild)	18	A	possible

IN - VITRO STUDIES:

Dissolution Testing:

The dissolution testing was conducted according to the method in the USP/NF 23/18, 1995, on 12 units each of 300 mg, and 150 mg strength tablets of the test and reference products in 900 mL of water, apparatus 2 with a rotation speed of 50 rpm. NLT [redacted] (Q) of the labeled amount of ranitidine was dissolved in 45 minutes, and no unit was less than (Q - 15%) (Table 5).

Assay Potency:

The mean potencies were 98.1% and 95.6% for Ranitidine Tablets, 150 mg (lot #100315) and 300 mg (lot #100316), respectively.

The mean potencies were 95.9% and 96.0% for Zantac Tablets, 150 mg (lot #Z11823LP) and 300 mg (lot #Z11583KP), respectively.

Content Uniformity:

The mean content uniformity of the test product, 150 mg tablets (lot# 100315) was 98.9% with a range of 96.6% - 101% (N=10, CV=1.3%).

The mean content uniformity of the test product, 300 mg tablets (lot# 100316) was 97.0% with a range of 95.1% to 99.5% (N=10, CV=1.4%).

WAIVER REQUEST OF BIOEQUIVALENCE STUDY FOR RANITIDINE TABLETS, USP, 150 MG:

The firm has requested waiver of bioequivalence study requirements for its test product, Ranitidine Tablets, USP, 150 mg (batch size: [redacted] tablets) based on the following:

(a) Comparative single dose bioequivalence study conducted on the highest strength of Ranitidine Tablets, USP, 300 mg and Zantac Tablets, 300 mg.

(b) Comparative dissolution testing conducted on Ranitidine Tablets and Zantac Tablets, 300 mg and 150 mg (Table 5).

(c) Similarity of the formulations of the firm's Ranitidine Tablets, 300 mg and 150 mg (Table 6).

COMMENTS:

1. The 90% confidence intervals for the pharmacokinetic parameters fall within the required range established by the Division of Bioequivalence.

2. There are no product and period effect (p=0.05) observed for the Ln-transformed or un-transformed parameters.

3. There is a sequence effect (p=0.1) for AUC(0-T): [p=0.0388]; Ln AUC(0-T): [p=0.0574]; AUC(0-Inf): [p=0.0419]; Ln AUC(0-Inf): [p=0.0606]; and C(Max): [p=0.0515]; LnC(Max): [p=0.0732].

However, according to the Division of Bioequivalence Guidance titled: "Statistical Procedures for Bioequivalence Studies Using a

Standard Two-Treatment Crossover Design" (July 01, 1992) the sequence effect may be acceptable since the following were met:

a) The study was a single dose study;
b) Only healthy, normal subjects completed the study;
c) The drug was not an endogenous entity;
d) Washout period of one week was long enough between the two phases (mean elimination half-life was about 3 hours for both test and reference products), and there was no detectable ranitidine level in predose samples of any of the subjects;
e) All scientific and statistical criteria were met;
f) The assay methodology was valid and acceptable;
g) The data were acceptable; and
h) Statistical data analyses were appropriate and the parameters met the confidence intervals criteria.

4. Lot #100316 (test product) and #Z11583KP (reference product) were used for both, the bioequivalence study and the dissolution testing. The test product batch size was [redacted] tablets.

5. No errors were found by spot checking of the calculations and statistical data analysis.

6. Some of the subjects showed more than one peak in the plasma concentration-time profiles for both test and reference products.

7. Inactive ingredients of the test products, Ranitidine Tablets, 150 and 300 mg are similar to the inactive ingredients of the reference products, Zantac Tablets, 150 and 300 mg (Table 6).

DEFICIENCIES: None.

RECOMMENDATIONS:

1. The single dose bioequivalence study under fasting conditions submitted by Genpharm Inc. Pharmaceuticals on its Ranitidine Tablets, 300 mg lot #100316 comparing it to Zantac Tablets, 300 mg, lot #Z11583KP has been found acceptable by the Division of Bioequivalence.

2. The dissolution testings conducted by Genpharm Inc. Pharmaceuticals on its Ranitidine Tablets, 300 mg (lot #100316) and 150 mg (lot #100315) are acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than [redacted] of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

4. Waiver of bioequivalence study requirements for Ranitidine Tablets, 150 mg is granted.

[redacted]

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE [redacted]
FT INITIALED RMHATRE [redacted] 7/18/95

Concur: [redacted] Date: 8/1/95

Keith Chan, Ph.D.
Director
Division of Bioequivalence

FNouravarsani/07-17-95/74023SDW.N94

CC: ANDA #74-023 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-658 (Mhatre, Nouravarsani), Drug File, Division File.

Table 1:

Mean (CV%) Serum Concentrations (ng/mL) of Ranitidine, N=26:

Time, hr	Test Product	Reference Product
0.00	000.00 (--)	000.00 (--)
0.33	124.82 (83)	117.62 (93)
0.67	419.69 (63)	364.68 (63)
1.00	499.27 (52)	451.94 (62)
1.33	568.69 (50)	541.72 (61)
1.67	718.04 (62)	628.52 (65)
2.00	752.62 (50)	720.38 (56)
2.50	841.19 (39)	772.19 (49)
3.00	828.96 (36)	825.04 (41)
3.50	740.69 (36)	769.00 (37)
4.00	645.00 (32)	718.54 (37)
5.00	490.27 (36)	558.62 (45)
6.00	368.77 (32)	399.27 (36)
8.00	210.54 (31)	236.23 (32)
10.00	127.36 (36)	140.44 (31)
12.00	72.62 (38)	80.90 (34)
16.00	31.12 (48)	31.10 (41)
20.00	12.22 (84)	13.29 (68)

Table 2:

Comparison of Mean (CV%) Ranitidine Pharmacokinetic Parameters Obtained for the Test and Reference Products, N=26:

			90% CI	
Parameters	Test	Reference	Ln-trans.	Un-trans.
AUC(0-T) hr*ng/mL	4855.2(25)	5021.3(27)	91 - 105	90 - 103
AUC(0-Inf) hr*ng/mL	4931.6(25)	5094.0(27)	91 - 105	91 - 103
C(Max) ng/mL	1090.1(34)	1075.4(32)	91 - 114	92 - 111
T(Max) hr	2.62(34)	2.79(36)		
K(Elm) 1/hr	0.23881(15)	0.24238(14)		
T(1/2) hr	2.96(15)	2.91(14)		

Table 3: AUC(0-T)/AUC(0-Inf) Percentage

Subject #	Test	Reference
1	[redacted]	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		
26		
Mean%	98.4	98.6
CV%	0.7	0.9
Range%	97.0-99.0	95.0-99.0

Table 4: Ratio Analysis of the Parameters

Subject	(Test/Reference) Percentage AUC(0-T)	AUC(0-Inf)	C(Max)
1	[redacted]		
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
Mean%	99.7	99.7	106.9
CV%	21.2	20.6	28.3
Range%	53.0-156.3	54.3-155.5	34.9-184.0

Table 5: In Vitro Dissolution Testing

Drug (Generic Name): Ranitidine Tablets
Dose Strength: 300 mg and 150 mg
ANDA: #74-023
Firm: Genpharm Inc.
Submission Date: November 30, 1994

I. Conditions for Dissolution Testing:

USP XXII Basket___ Paddle X RPM 50 No. Units Tested 12

Medium: water at 37° C Volume: 900 mL

Reference Drug: Zantac Tablets

Assay Methodology: [redacted]

II. Results of In Vitro Dissolution Testing:

Sampling Times minutes	Test: Ranitidine Tablets Lot #100316 Strength (mg) 300			Reference: Zantac Tablets Lot #Z11583KP Strength (mg) 300		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
05	40.4	[redacted]	(27.1)	31.4	[redacted]	(12.6)
10	75.9		(09.7)	59.8		(07.4)
15	90.4		(03.6)	78.1		(03.5)
20	95.0		(01.2)	89.0		(01.7)
30	95.7		(01.3)	95.4		(00.9)
45	96.4		(01.2)	96.6		(01.1)

Sampling Times minutes	Test: Ranitidine Tablets Lot #100315 Strength (mg) 150			Reference: Zantac Tablets Lot #Z11823LP Strength (mg) 150		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
05	18.5	[redacted]	(50.1)	16.4	[redacted]	(18.5)
10	48.7		(32.3)	36.7		(07.8)
15	80.4		(14.3)	54.2		(04.9)
20	96.0		(01.8)	70.1		(05.4)
30	97.4		(01.3)	86.7		(06.0)
45	97.4		(01.2)	95.1		(01.1)

Table 6:

Formulation Comparison of 300 and 150 mg Tablets of the Test (T) and Reference (R) Products:

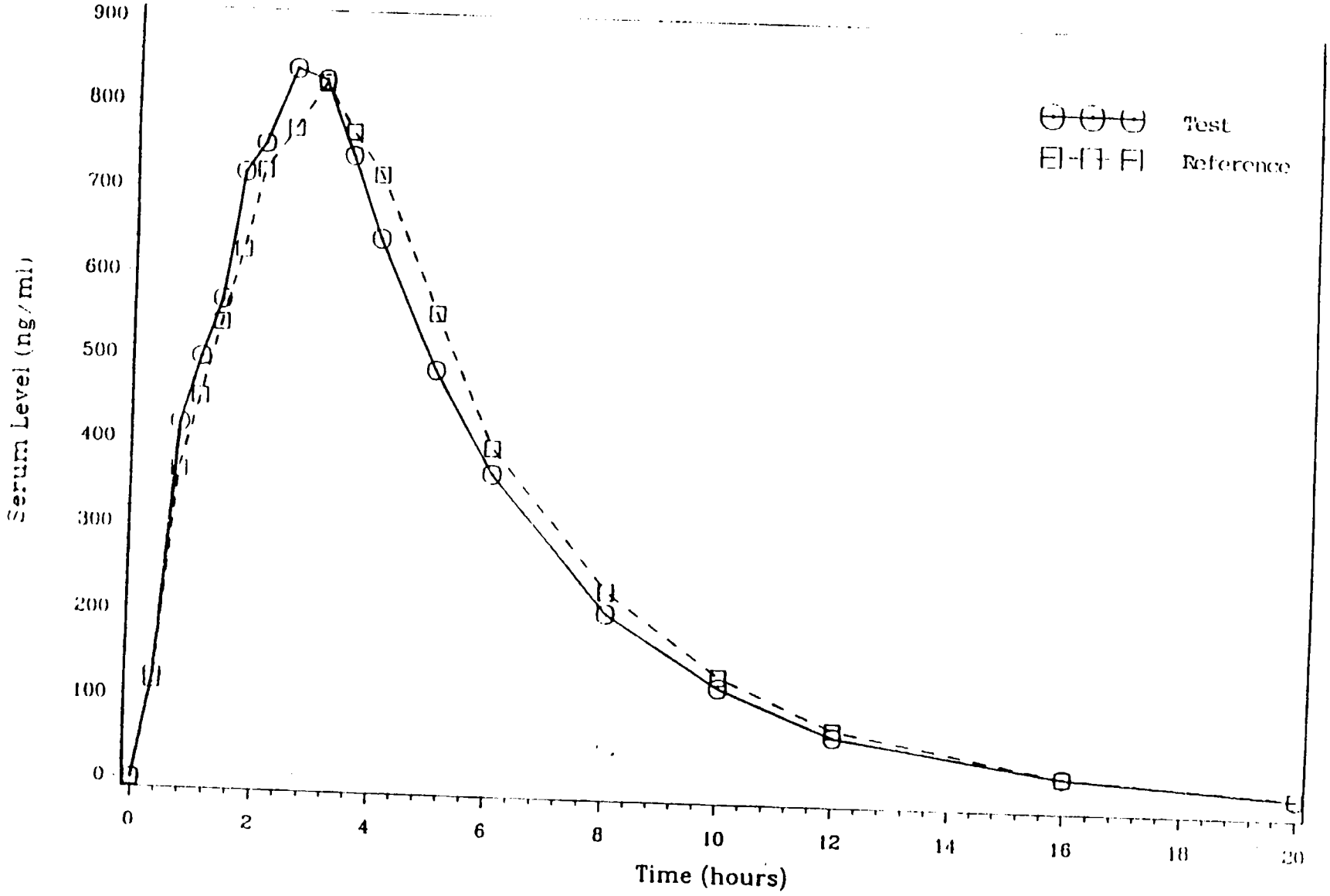
Ingredients	T, 300mg	T, 150mg	R, 300mg	R, 150 mg
Ranitidine HCl	336.00mg	168.00mg	336.00mg	168.00mg
Microcrystalline Cellulose	[redacted]			
Crosscarmellose Sodium				
Magnesium Stearate				
[redacted] Orange				
White				
Components of [redacted] Orange and/or [redacted] White:				
Hydroxypropyl Methylcellulose	[redacted]			
Titanium Dioxide				
Polydextrose				
Triethyl Citrate				
Polyethylene Glyco				
FD & C Yellow #6 [redacted]				
Yellow Iron Oxide				
Triacetin				
D & C Yellow #10 [redacted]				

X = present in the formulation

-- = not present in the formulation

Figure 1: Mean Ranitidine Serum Levels

n = 26



Ranitidine Hydrochloride
Tablets, USP, 150 mg
ANDA #74-023

SPONSOR:
Genpharm Pharmaceutical Inc.
37 Advance Road
Etobicoke, Ontario
CANADA M8Z 2S6

SEP 23 1992

AGENT:
Dr. Steven Wentworth
6701 Democracy Blvd.
Suite 300
Bethesda, MD 20817

Dear Dr. Wentworth:

Reference is made to the in vivo bioequivalence study and in vitro dissolution data which you submitted on March 12, 1992 in support of Genpharm's ranitidine hydrochloride tablets, 150 mg.

The material has been reviewed by the Division of Bioequivalence and we have the following comments:

DEFICIENCIES:

1. [redacted]

2.

3. [redacted]

4. Total of 67 samples were diluted 2 times or more. The original values of these samples should be reported.

5. The batch size of the test product should be reported.

RECOMMENDATION:

The bioequivalence study submitted by Genpharm Inc. Pharmaceuticals on its ranitidine, 150 mg, tablets, Lot # T11-3-150 comparing it to Glaxo Pharmaceuticals, Zantac, 150 mg, Tablets, Lot # Z12350NP has been found incomplete by the Division of Bioequivalence for the reasons enumerated above.

All responses and correspondence with regard to this letter should be sent to the Office of Generic Drugs, HFD-630.

Sincerely yours,

Shrikant V. Dighe, Ph.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

cc: Date _____
HFD-632 Pollock/Branch 6
HFD-650 (Dighe, Greenberg, CST)
stm 08-13-92 (N74023.STD)
bio letter

Ranitidine Hydrochloride
Tablets, USP, 150 & 300 mg
ANDA #74-023

AGENT:
Dr. Steven D. Wentworth
Pharmaceutical Consultant
11412 Empire Lane
Rockville, MD 20852

FEB 5 1992

SPONSOR:
GenPharm Pharmaceuticals, Inc.
37 Advance Road
Etobicoke, Ontario,
CANADA M8Z 2S6

Dear Dr. Wentworth:

Reference is made to the in vivo bioequivalence study, waiver request and supporting dissolution data submitted on February 4, 1991 in support of your ranitidine hydrochloride tablets.

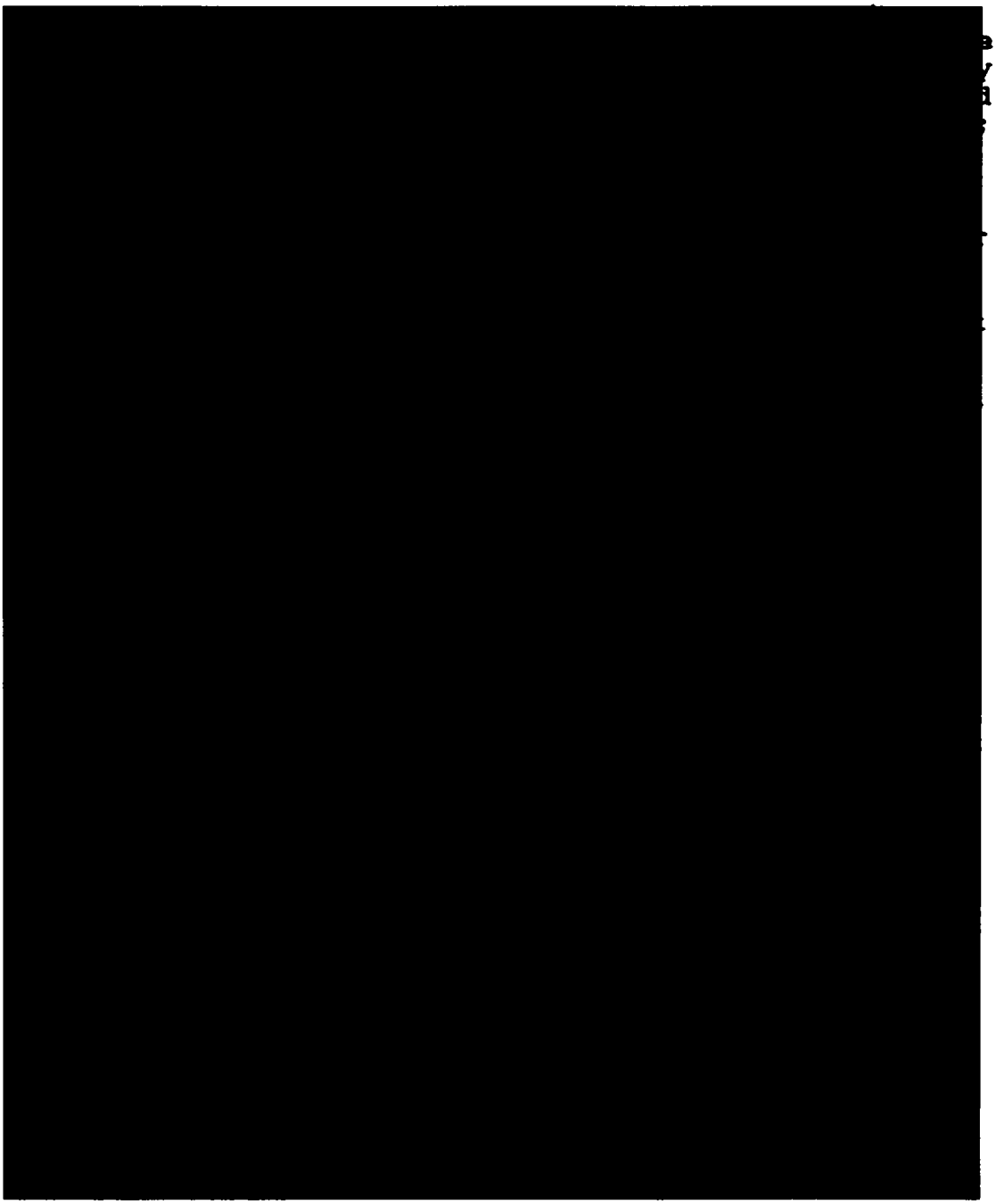
The material has been reviewed by the Division of Bioequivalence and we have the following comments:

DEFICIENCIES:

1. The results of the during - study assay validation show that a significant number of standard curves and quality control samples were not acceptable or were reported incorrectly, summarized as following:

   A. [redacted]

B.



C.

D.

E.

2. The summary of the pre - study assay validation to determine ranitidine in serum has not been submitted for review.

3. Samples with concentrations above quantifiable limit were diluted before reassaying. The original values of <u>some</u> of these samples were not reported.

4. There is no report of the assayed potency for the Reference product. The assayed potency of the Test product should not differ more than 5% of the one obtained for the Reference product.

5. The request for a waiver of bioequivalence study requirements for 150 mg ranitidine tablets is not granted, since the firm has not conducted an acceptable bioequivalence study on the higher strength of the ranitidine tablets (300 mg). Furthermore, the comparative dissolution testing conducted on the 150 mg ranitidine tablets and 150 mg Zantac Tablets is not acceptable. The deviations obtained between the means of the test and reference products are very high at all time intervals except for the 30 - 44 minutes interval. The coefficient of variation (CV) of higher than 5% obtained for the last time interval is also unacceptable.

RECOMMENDATIONS:

1. The results of the bioequivalence study submitted by Genpharm Pharmaceuticals on its ranitidine tablets, 300 mg, Lot # T11-5-300 comparing it to Glaxo Pharmaceuticals, Zantac^{R} Tablets, 300 mg, Lot # Z10650DP has been found unacceptable by the Division of Bioequivalence.

2. Your request for a waiver of bioequivalence study requirements for ranitidine tablets, 150 mg, is denied. See DEFICIENCY 5.

All responses and correspondence with regard to this letter should be sent to the Office of Generic Drugs, HFD-630.

Sincerely yours,

Shrikant V. Dighe, Ph.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

cc: Date _____
HFD-632
Pollock, HFD-650 (Dighe, CST)
lsg 12-23-91 (N74023.STD)
bio letter

12/16/91

Ranitidine Hydrochloride
Tablets, USP, 150 & 300 mg
ANDA #74-023
Reviewer: F. Nouravarsani
74023SDW.291

Genpharm Pharmaceuticals, Inc.
Ontario, Canada
Submission Date:
February 04, 1991

Review of a Bioequivalence Study, Dissolution Testing and a Waiver Request

INTRODUCTION:

Genpharm Pharmaceuticals, Inc. has submitted results of a comparative bioequivalence study and dissolution testing conducted on its Test product, Ranitidine Hydrochloride Tablets, 300 mg, and Zantac^{R} Tablets, 300 mg, manufactured by Glaxo Pharmaceuticals (NDA #18703-002) as the listed Reference product.

Ranitidine hydrochloride, a histamine H_2-receptor antagonist inhibits daytime and nocturnal basal gastric acid secretions. it also inhibits the gastric acid secretion stimulated by meal, pentagastrin, and betazole. The oral absolute bioavailability of Zantac is 50% . Mean peak levels of ranitidine are 440 to 545 ng/mL observed at 2 to 3 hours following a 150 mg dose. The administration of food or antacids does not show a significant effect on the absorption of the zantac. The elimination half-life is reported to be 2.5 to 3 hours.

BIOEQUIVALENCE STUDY:

Objectives:

1. Determine the bioequivalency of the Test product, Ranitidine Hydrochloride Tablets, 300 mg and the Reference product, Zantac^{R} Tablets, 300 mg, under fasting conditions.

2. Compare the in-vitro dissolution testing conducted on the Test and Reference products.

3. Request a waiver of bioequivalence study requirements for 150 mg Ranitidine Hydrochloride Tablets.

Sponsor: Genpharm Pharmaceuticals, Inc. The firm has appointed Steven Wentworth, Ph.D. as a United States agent to Genpharm for this submission.

Manufacturer: Genpharm Pharmaceuticals

[redacted]

[redacted]

Study Design:

A single dose of treatment A (Test product, lot #T11-5-300) and treatment B (Reference product, lot #Z10650DP, expiration date of October 1992) were administered randomly to healthy volunteers in a two - way crossover study design (project No. 13088).

Clinical Study Dates:

Phase I: October 26-28, 1990
Phase II: November 02-04, 1990
Washout period: 7 days

Subjects:

Twenty six (26) healthy male volunteers completed the study. Subjects 25 and 26 participated as possible replacements for drop outs. Subject number 1, 3, 4, 5, 7, 9, 13, 14, 16, 17, 18, 21, and 25 received treatment A for phase I study. The rest of the volunteers (2, 6, 8, 10, 11, 12, 15, 19, 20, 22, 23, 24, and 26) were dosed treatment A for phase II. The subjects were selected based on their health history, clinical laboratory tests and physical examinations. Subjects #6, #17, #23, #25, and #26 were smokers. The range of the subjects age, weight, and height are summarized as following:

Age: 19 - 50 years
Weight: 138 - 216 pounds
Height: 66 - 76 inches

Housing, Food and Fluid Intake:

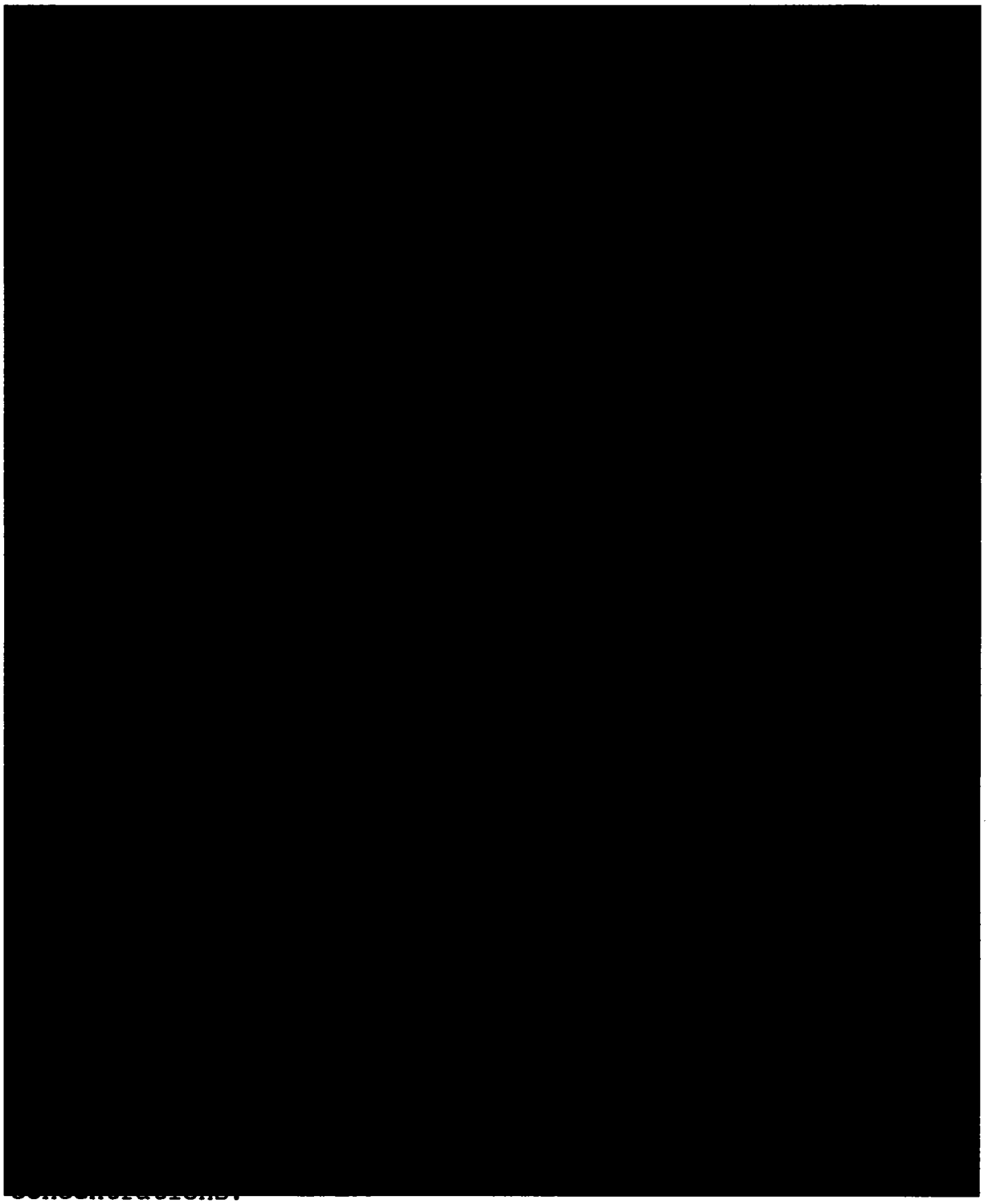
All volunteers were housed in the [redacted] Research unit 11 hours prior to the fasting and during the blood sample collection periods. The subjects fasted overnight prior to the dosing and 5 hours following the dose administration. The dose was taken with 240 mL of water. The standard meals were served five hours after the dose.

Blood Samples:

Blood samples of 10 mL were collected at predose, 0.33, 0.67, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0 hours, and were stored at -20° C until analysis.

Analytical Procedures:

[redacted]



Statistical Analysis:

The data were analyzed using SAS - GLM procedure. The two one sided t-test procedure (90% confidence interval) was used to compare the pharmacokinetic parameters of AUC(0-TLQC), AUC(0-Inf), and C(Max) obtained from the Test and the Reference products.

Results:

The mean serum concentrations of ranitidine obtained for the Test and Reference products are summarized in Table 1. Figure 1 shows plots of the mean plasma concentrations of ranitidine versus time for both, Test and Reference products. The mean of the pharmacokinetic parameters obtained for both, Test and Reference products are compared in Table 2.

The Test product AUC(0-TLQC) and AUC(0-Inf), 5133.4 hr*ng/mL and 5172.6 hr*ng/mL respectively are comparable with those obtained for the Reference product 5002.0 hr*ng/mL and 5044.9 hr*ng/mL respectively.

The mean C(Max) value of 1183.5 ng/mL obtained for the Test product is also comparable with the mean C(Max) value of 1167.9 ng/mL obtained for the Reference product.

The 90% confidence intervals (CI) for the parameters of AUC(0-TLQC), AUC(0-Inf), and C(Max) fall in the range required by the Division of Bioequivalence. No sequence effects are observed for the parameters using SAS-GLM procedure.

Parameter	90% CI		Test/Reference%
AUC(0-TLQC)	95.6	109.2	102.6
AUC(0-Inf)	95.6	109.0	102.5
C(Max)	92.1	109.8	101.3

IN - VITRO STUDIES:

Formulation:

Ingredient	150 mg Tablets	300 mg Tablets
Ranitidine HCl	168 (a)	336 (b)
Croscarmellose Sodium	[redacted]	
magnesium Stearate		
Microcrystalline Cellulose		
Opadry Clear YS-1-70[redacted]		
Hydroxypropyl Methylcellulose		
Polyethylene Glycol		
Titanium Dioxide		
Tablet Weight	310	490

(a) = as 150 mg ranitidine
(b) = as 300 mg ranitidine
(c) = not presented in the formulation
(d) = present in the formulation, but quantitative formulation is not available

Dissolution Testing:

Results of the dissolution testing conducted on 12 units of the same lots of the test (#T11-5-300) and reference (#Z10650DP) products used in the bioequivalence study are shown in Table 3. Over [redacted] mean of 12 units) of the labeled amounts of the ranitidine was dissolved in 44 minutes for the Test and Reference products. The dissolution of no units was less than Q - 15% . The CV% obtained for both, the Test and Reference products at 30 - 44 minutes interval are less than 5% . The differences between means of the Test and Reference products are less than 10% for all of the time intervals except for the first one, which is 15.2% . This difference is less than 20%, and is acceptable for the first time interval.

Potency:

A mean value of 99.2% (stated in chemistry section, volume 1.1a, page 467) was obtained for Ranitidine Tablets from assay of the Test product. The assayed potency of the Reference product was not stated.

Waiver Request for 150 mg Ranitidine Tablets:

The firm has requested for a waiver of bioequivalence study requirements for its 150 mg Ranitidine Tablets under 21 CFR section 320.22 (d)(2).

The results of dissolution testing conducted on the Test product, Ranitidine Tablets, 150 mg (Lot #T11-3-150) and the Reference product, Zantac, 150 mg (Lot #Z10179BP) are summarized in Table 3. Over [redacted] of the labeled amount of the ranitidine was dissolved in 44 minutes (mean of 12 tablets) for the Test product, and there was no unit with a dissolution of Q - 15% . The mean of the dissolution of 12 units of the reference product (Q=[redacted] is slightly less than [redacted]. There is no unit with a dissolution of less than Q - 15%. The deviations of means of the Test product from the Reference product are more than 10% for the time intervals of 0 - 10 minutes (60.9%), 10 - 20 minutes (50%), and 20 - 30 minutes (31%). The difference between the means at the last time interval, 30 - 44 minutes is 9.7% . The CV% at this time interval is slightly higher than 5% for both Test (6.1%) and Reference (5.8%) products.

COMMENTS:

1. Lots #T11-5-300 (Test product) and #Z10650DP (Reference product) were used for both, the bioequivalence study and the dissolution testing. The Test product batch size was [redacted] tablets.

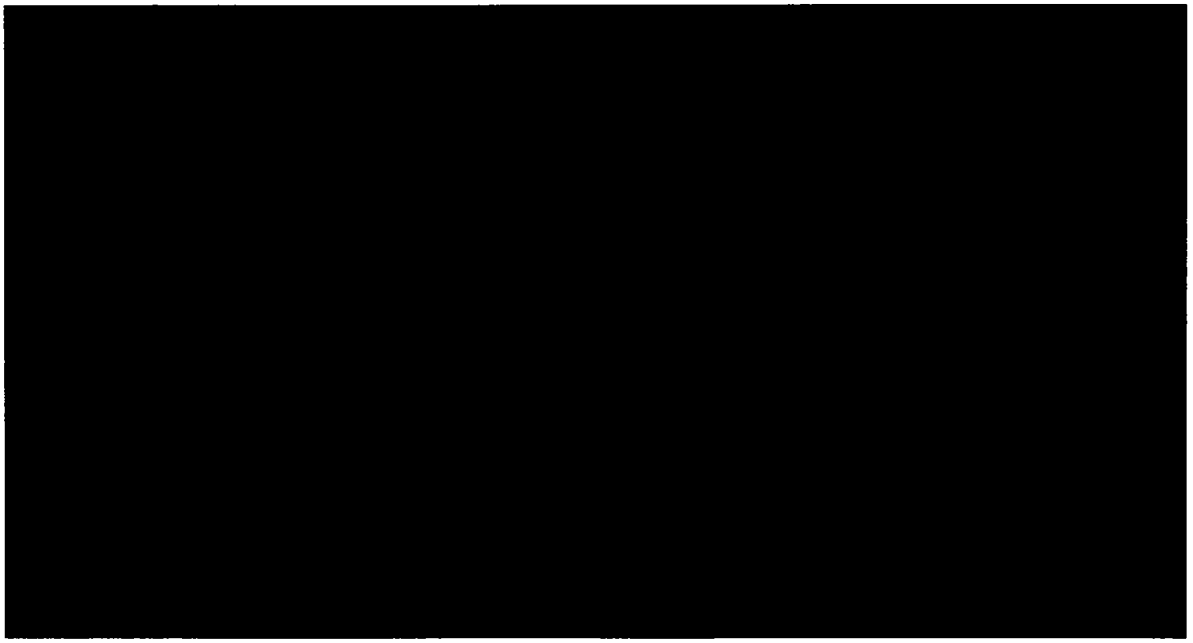
2. The results of the dissolution testing conducted on 300 mg Ranitidine Tablets are acceptable.

[redacted]

DEFICIENCIES:

1. The results of the during - study assay validation show that a significant number of standard curves and quality control samples were not acceptable or were reported incorrectly, summarized as following:

[redacted]



2. The summary of the pre - study assay validation to determine ranitidine in serum has not been submitted for review.

3. Samples with concentrations above quantifiable limit were diluted before reassaying. The original values of some of these samples were not reported.

4. There is no report of the assayed potency for the Reference product. The assayed potency of the Test product should not differ more than 5% of the one obtained for the Reference product.

5. The waiver request of bioequivalence study requirements for 150 mg Ranitidine Tablets is not granted, since the firm has not conducted an acceptable bioequivalence study on the higher strength of the Ranitidine Tablets, 300 mg. Furthermore, the comparative dissolution testing conducted on the 150 mg Ranitidine Tablets and 150 mg Zantac Tablets is not acceptable. The deviations obtained between the means of the Test and Reference products are very high at all time intervals except for the 30 - 44 minutes interval. The obtained coefficient of variation (CV) of higher than 5% for the last time interval is also unacceptable.

RECOMMENDATIONS:

1. The results of the bioequivalence study submitted by Genpharm Pharmaceuticals on its Ranitidine, 300 mg, Tablets, Lot # T11-5-300 comparing it to Glaxo Pharmaceuticals, Zantac^{R}, 300 mg, Tablets, Lot # Z10650DP has been found unacceptable by the Division of Bioequivalence. The firm should be informed of the DEFICIENCIES #1 - #4.

2. The dissolution testing conducted by the Genpharm Pharmaceuticals on its Ranitidine, 300 mg, Tablets, Lot # T11-5-300 is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of water at 37° C using USP XXII apparatus II (paddle) at 50 rpm. The Test product should meet the following specifications:

Not less than [redacted] of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

4. The firm's request for a waiver of bioequivalence study requirements for its 150 mg Ranitidine Tablets is not granted. The firm should be informed of the DEFICIENCY #5.

The firm should be informed of the DEFICIENCIES and the RECOMMENDATIONS.

[redacted]

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE [redacted]
FT INITIALED RMHATRE [redacted]

Concur: [redacted] Date: 12/13/91

Shrikant V. Dighe, Ph.D.
Director
Division of Bioequivalence

FNouravarsani/rlh/05-10-91/WP 74023SDW.291

CC: ANDA #74-023 Original, HFD-630, HFD-600 (Williams), HFD-604 (Hare), HFD-22 (Hooton), HFD-658 (Mhatre, Nouravarsani), Drug File.

Table 1

Mean (CV%) serum Concentrations (ng/mL) of Ranitidine:

Time, hr	Test Product	Reference Product
0.00	000.0 (00.0)	000.0 (00.0)
0.33	106.3 (68.2)	118.9 (82.9)
0.67	309.0 (43.1)	320.0 (30.4)
1.00	405.3 (38.7)	389.9 (29.6)
1.50	569.7 (59.1)	626.1 (54.1)
2.00	775.9 (50.4)	858.9 (59.6)
2.50	918.4 (41.8)	927.3 (47.4)
3.00	885.4 (35.9)	827.6 (35.7)
3.50	812.6 (33.6)	796.6 (32.9)
4.00	731.7 (35.4)	638.0 (27.6)
6.00	402.0 (30.5)	387.6 (25.1)
8.00	230.3 (32.1)	217.0 (25.4)
10.00	131.4 (38.6)	127.7 (28.0)
12.00	76.5 (44.1)	78.3 (43.2)
16.00	29.5 (82.7)	27.2 (44.5)
24.00	4.7 (93.6)	5.9 (64.4)

Table 2

Comparison of the Mean (CV%) Pharmacokinetics Parameters for Ranitidine Obtained for the Test and Reference Products:

Parameters	Test Product	Reference Product
AUC(0-TLQC) hr*ng/mL	5133.4 (21.7)	5002.0 (18.0)
AUC(0-Inf) hr*ng/mL	5172.6 (21.5)	5044.9 (17.9)
C(Max) ng/mL	1183.5 (29.7)	1167.9 (34.9)
T(Max) hr	2.80 (27.5)	2.77 (34.3)
K(El) 1/hr	0.2647 (18.2)	0.2460 (13.8)
T(1/2) hr	2.70 (16.7)	2.86 (12.9)

Drug (Generic Name): Ranitidine HCl Firm: Geneva Pharm.
Dose Strength: 150 & 300 mg Tablets
ANDA # 74023 Submission Date: February 4, 1991

Table 3 - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXII Basket ____ Paddle ✓ RPM 50 No. Units Tested: 12

Medium: Water, 37° ± 0.5 C Volume: 900 ml

Reference Drug; (Manuf.): Zantac, Glaxo Pharm.

Assay Methodology: [redacted]

II. Results of In-Vitro Dissolution Testing:

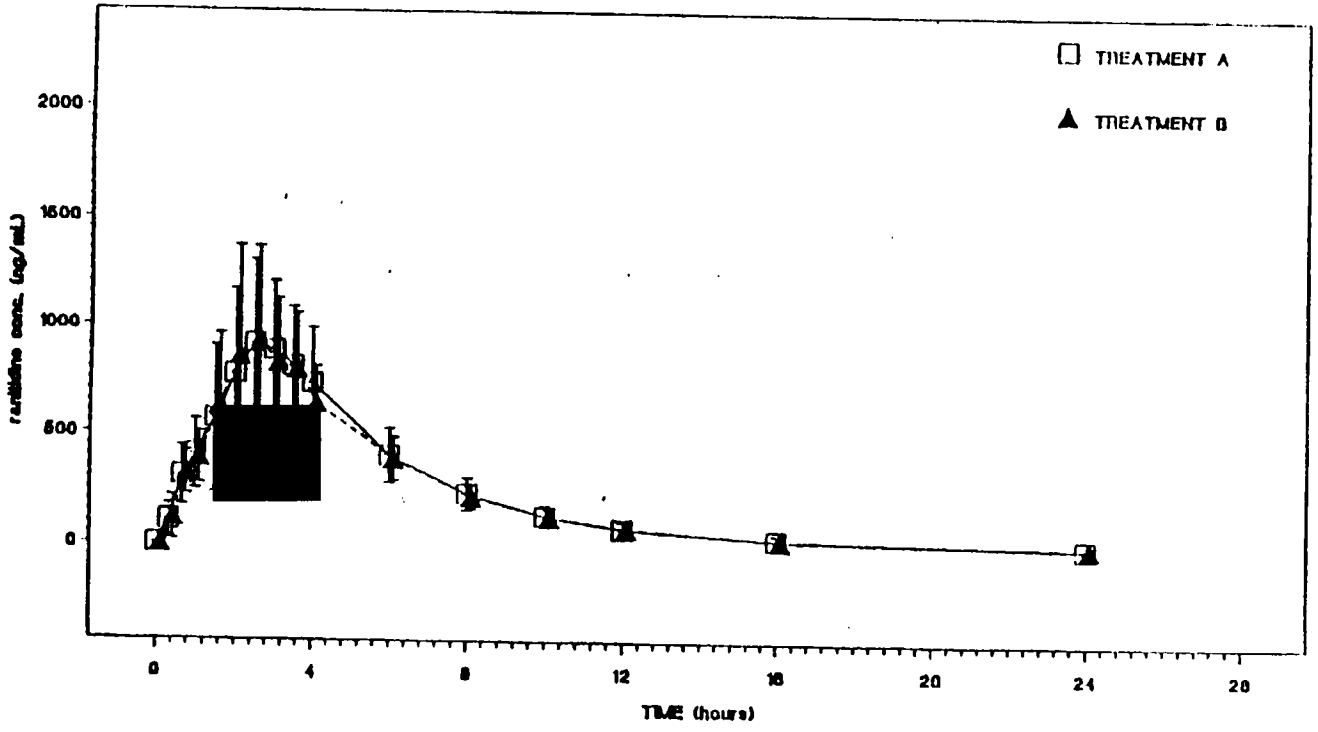
Sampling Times (Min.) ~~(Hr.)~~	Test Product Ranitidine HCl Lot # T11-5-300 Strength (mg) 300 Mean % Dissolved	Range	(CV)%	Reference Product Zantac Lot # Z10650DP Strength (mg) 300 Mean % Dissolved	Range	(CV)%
10	36.4	[redacted]	(11.4)	31.6	[redacted]	(6.3)
20	78.3		(7.2)	72.9		(15.6)
30	91.3		(4.7)	86.1		(7.5)
44	93.1		(3.8)	91.7		(3.9)
____	____	____	( )	____	____	( )

Sampling Times (Min.) ~~(Hr.)~~	Test Product Lot # T11-3-150 Strength (mg) 150 Mean % Dissolved	Range	(CV)%	Reference Product Lot # Z10179BP Strength (mg) 150 Mean % Dissolved	Range	(CV)%
10	28.8	[redacted]	(27.0)	17.9	[redacted]	(10.6)
20	58.2		(21.6)	38.3		(11.2)
30	80.7		(9.5)	61.6		(8.4)
44	87.3		(6.1)	79.6		(5.8)
____	____	____	( )	____	____	( )

Figure 1

[redacted]
TREAT A = Ranitidine Tablets, 300 mg [redacted]
TREAT B = Zantac(R) Tablets, 300 mg [redacted]
ranitidine in serum

FIGURE 1
MEAN (S.D.) OF ALL VOLUNTEERS



LINEAR SCALE
TREATMENT B HAS BEEN OFFSET 0.1 HOURS TO FACILITATE VIEWING

ANDA 74-023

Lipha Pharmaceuticals, Inc.
U.S. Agent for Genpharm, Inc.
Attention: Anita M. Goodman
9 West 57th Street, Suite 3825
New York, NY 10019-2701

MAY 16 1997

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Ranitidine Hydrochloride Tablets, 150 and 300 mg (Form 1).

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MAY 12 1997

Ranitidine Hydrochloride (Form 1)
Tablets, 150 and 300 mg
ANDA #74-023
Reviewer: F. Nouravarsani
74023SDW.996

Genpharm Inc. Pharmaceuticals
Ontario, Canada
Submission Date:
September 27, 1996
December 16, 1996
February 17, 1997
March 03, 1997, and
March 20, 1997

Review of a Fasting Bioequivalence Study, Dissolution Testing, and a Waiver Request

Genpharm Inc. Pharmaceuticals has submitted a comparative fasting bioequivalence study and dissolution testing conducted on its test product, Ranitidine Hydrochloride (Form 1) Tablets, 150 mg, and Zantac^{R} Tablets, Ranitidine Hydrochloride, 150 mg, manufactured by Glaxo Pharmaceuticals (NDA #18703-001) as the listed reference product. The firm has also requested for a waiver of bio-study for its test product, 300 mg Ranitidine Hydrochloride (Form 1) Tablets (Submission Dates: September 27 and December 16, 1996).

The firm has also submitted additional information requested by phone call from the Division of Bioequivalence as follows:

1. Dissolution testing method and proposed specifications, contents uniformity for 150 and 300 mg tablets, assayed Potencies for 150 and 300 mg tablets, and batch size of lot used in the bio-study (Submission Date: February 17, 1997).

2. Reasons for reanalyzing samples from subjects #12 and #16, and reinjecting samples from subjects #14 and #21. The available original data were also submitted (Submission Dates: March 03, and March 20, 1997).

INTRODUCTION:

Ranitidine hydrochloride is a polymorphic compound, and it is found in two forms of 1 and 2. Pharmacokinetic study conducted on the Ranitidine Hydrochloride Tablets, Forms 1 and 2 by Glaxo Group Research, LTD. showed the bioequivalency of the two Forms. There was no difference between the extent, rate, or elimination half-life of the products under the study (NDA #18-703 and Shen, J., Lee, D., and McKeag, R., Bioequivalence of Two Forms of Ranitidine, New Zealand Pharmacy, October 1995, p 24-25).

Ranitidine HCl is freely soluble in water and acetic acid (The

Merck Index, 11th Edition), and both forms have almost identical dissolution rates, and generate identical forms in solution, therefore, the two forms must be bioequivalent (Shen, J., Lee, D., and McKeag, R., Bioequivalence of Two Forms of Ranitidine, New Zealand Pharmacy, October 1995, p 24-25).

A three-way, cross-over, bio-study conducted by [redacted] (Canada) comparing marketed Apo-Ranitidine containing Form 1 (300 mg Tablets) with two brand-name formulations containing ranitidine Form 2 (300 mg) showed bioequivalency between the three products (Shen, J., Lee, D., and McKeag, R., Bioequivalence of Two Forms of Ranitidine, New Zealand Pharmacy, October 1995, p 24-25).

Ranitidine hydrochloride, a histamine H_2-receptor antagonist inhibits daytime and nocturnal basal gastric acid secretions. It also inhibits the gastric acid secretion stimulated by meal, pentagastrin, and betazole. The oral absolute bioavailability of Zantac is 50%. Mean peak levels of ranitidine are 440 to 545 ng/mL observed at 2 - 3 hours following a 150 mg dose. The elimination half-life is reported to be 2.5 to 3 hours.

The administration of food or antacids does not show a significant effect on the absorption of Zantac (PDR, 1996).

OBJECTIVES:

1. Determine the bioequivalency of the test product, Ranitidine Hydrochloride (Form 1) Tablets, 150 mg and the reference product, Zantac^R Tablets, 150 mg under fasting conditions.

2. Compare the in-vitro dissolution testing conducted on the test and reference products.

3. Request a waiver of bioequivalence study for its test product, 300 mg Ranitidine Hydrochloride (Form 1) Tablets.

BIOEQUIVALENCE STUDY:

Sponsor: Genpharm Inc. Pharmaceuticals, Ontario, Canada.

[redacted]

Study Design:

A single dose of each test and reference products were administered randomly to healthy volunteers in an open - label, two - way crossover study design under fasting conditions (project No. 106-24-10899).

Treatments:

Treatment A (test Product): A single dose of Ranitidine Hydrochloride (Form 1) Tablets, 150 mg, Lot #101030/Bulk Lot: #100861, batch size of [redacted] units.

Treatment B (reference Product): A single dose of Zantac^{R}, Ranitidine Hydrochloride Tablets, 150 mg, Lot #5ZPT009, Expiration date: January 1997.

Clinical Study Dates:

Phase I: April 14-16, 1995
Phase II: April 21-23, 1995
Washout period: one week

Subjects:

Twenty six (26) healthy male volunteers were enrolled in the study. Twenty-five (25) subjects completed the study. Subject #10 (sequence 2) did not return for phase II of the study. Subjects number 2, 3, 5, 8, 9, 11, 14, 15, 18, 20, 21, 23, and 26 received treatment A for phase I study. The rest of the volunteers (1, 4, 6, 7, 12, 13, 16, 17, 19, 22, 24, and 25) were dosed treatment A for phase II. Subjects #5, 10, 13, 14, 19, 21, 22, 23, and 26 were smokers.

The subjects were selected based on their health history, clinical laboratory tests and physical examinations. The range of the subjects age, weight, and height are summarized as follows:

Age: 20 - 50 years
Weight: 136 - 212 pounds
Height: 66 - 78 inches

Housing and Fasting:

All volunteers were housed from approximately 12 hours prior to the dosing and during the blood sample collection until at least 20 hours post-dose. The subjects fasted overnight prior to the dosing for at least 10 hours, and 5 hours following the dose

administration. The dose was taken with 240 mL of water.

Blood Samples:

Blood samples of 10 mL were collected at predose, 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, and 20.0 hours after the dose.

Safety Monitoring:

Blood pressure and pulse rate were measured at pre-dose, 4 and 20 hours after the dose. Temperature and respiration rate were also determined at pre-dose, and 20 hours post-dose.

Analytical Procedures:

[redacted]

Statistical Analysis:

The data were analyzed using SAS - GLM procedure. The two one sided test procedure (90% confidence intervals) was used to compare the least square means of ln-transformed pharmacokinetic parameters of AUC(0-T), AUC(0-Inf), and C(Max) obtained from the test and the reference products.

Repeated Assay:

Samples from subjects #12 and #16 were reanalyzed, and samples from subjects #14 and #21 were reinjected. The firm was requested to submit original values of plasma levels and pharmacokinetics parameters, and Reason(s) for reassaying and reinjecting these samples. The firm's responses are as follows:

a. Samples from subject #12 were reanalyzed since the quality control (QC) samples were not acceptable (submission date: March 03, 1997). The original data for quality control samples were submitted on March 20, 1997. There was only one acceptable QC using the firm's SOP.

b. Samples from subject #16 were reassayed, since the elimination profiles for both phases were found to be inconsistant. The reassayed values were reported.

[redacted]

Results:

The mean serum concentrations of ranitidine obtained for the test and reference products are summarized in Table 1. No statistically significant difference is observed between the products at each sampling time except for 2 and 5 hours using SAS - GLM procedure alpha=0.05). Figure 1 shows plots of the mean plasma concentrations of ranitidine versus time for both, test and reference products. The mean of the pharmacokinetic parameters obtained for both, test and reference products are compared in Table 2.

The test product AUC(0-T) and AUC(0-Inf), 2172.0 hr*ng/mL and 2242.0 hr*ng/mL, respectively, are comparable with those obtained for the reference product, 2278.0 hr*ng/mL and 2344.0 hr*ng/mL, respectively. Range of percentage ratio of AUC(0-T)/AUC(0-Inf) are 92.0-98.0 for the test product, and 93.0-99.0 for the reference product (Table 3).

The mean C(Max) value of 430.8 ng/mL obtained for the test product is also comparable with the mean C(Max) value of 439.5 ng/mL obtained for the reference product.

The mean percentage of test/reference for the parameters of AUC(0-T), AUC(0-Inf), and C(Max) are 98.1, 98.4, and 101.1, respectively (Table 4).

The 90% confidence intervals (CI) for the least squares means, ln-transformed parameters of AUC(0-T), AUC(0-Inf), and C(Max) fall within the range (80% - 125%) required by the Division of Bioequivalence (Table 2).

Using SAS-GLM procedures, there is no period or treatment effect (alpha = 0.05) observed for each parameter, but there is a sequence

effect (alpha = 0.10). However, according to the Division of Bioequivalence Guidance titled: "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design" (July 01, 1992) the sequence effect may be acceptable since the following were met:

a) The study was a single dose study;
b) Only healthy, normal subjects completed the study;
c) The drug was not an endogenous entity;
d) Washout period of one week was long enough between the two phases (mean elimination half-life was about 3 hours for both test and reference products), and there was no detectable ranitidine level in predose samples of any of the subjects;
e) All scientific and statistical criteria were met;
f) The assay methodology was valid and acceptable;
g) The data were acceptable; and
h) Statistical data analyses were appropriate and the parameters met the confidence intervals criteria.

Adverse Effects:

The following subjects reported adverse events which were possibly related to the drug. The dose was given at 8:00 A.M.

Subject	Event	Severity	Product	Time
1	Frontal Headache	Mild	Genpharm	11:43
9	Headache, Upset Stomach, "Flushed" Feeling,	Moderate	Glaxo	13:00
	Vomiting	Mild	Glaxo	21:00
13	Bradycardia	Mild	Genpharm	11:58
26	Increased Blood Pressure	Mild	Glaxo	12:24

IN - VITRO STUDIES:

Dissolution Testing:

1. Results of the dissolution testing conducted on 12 units of the same lots of the test (Form 1, lot #100861) and reference (lot #5ZPT009) products, 150 mg, used in the bioequivalence study are shown in Table 5. Over [redacted] (mean of 12 units) of the labeled amount of the ranitidine was dissolved in 45 minutes for the test and reference products. Dissolution of the test product, ranitidine HCl, Form 1 is comparable with the dissolution of the product of ranitidine HCl, Form 2, lot #100315 (Table 5), which was granted a waiver of conducting a bio-study by the Division of Bioequivalence/OGD (dates: 8-1-95/8-16-95).

2. Results of the dissolution testing conducted on 12 units of the test (Form 1, lot #100862) and reference (lot #5ZPT001) products, 300 mg, are shown in Table 5. Over [redacted]mean of 12 units) of the labeled amount of the ranitidine was dissolved in 45 minutes for the test and reference products. Dissolution of the test product, ranitidine HCl, Form 1 is comparable with the product of ranitidine HCl, Form 2, lot #100316 (Table 5), which its bio-study was found acceptable by the Division of Bioequivalence/OGD (dates: 8-1-95/8-9-95).

3. The dissolution testing method was the same as the one reported in the USP 23, 1995.

Assay Potency:

The potencies were 100.1% (lot #100861) and 98.8% (lot #100862) for the 150 mg and 300 mg test products, respectively.

Content Uniformity:

The means content uniformity were 98.8% (CV%=1.7, N=10) for the 150 mg test product (lot #100861), and 98.2% (CV%=1.5, N=10) for the 300 mg test product (lot #100862).

Waiver Request of Bioequivalence Study for 300 mg Ranitidine HCl (Form 1) Tablts:

The firm has requested for a waiver of bioequivalence study requirements for its 300 mg Ranitidine HCl (Form 1) Tablets based on the followings:

a. The firm has an acceptable bioequivalence study and dissolution testing for the higher strength, 300 mg Ranitidine HCl (Form 2)

Tablets (ANDA #74023, submitted: November 30, 1994, review date: August 01, 1995).

b. The comparative dissolution testing conducted on the bio-study batch, 300 mg Ranitidine HCl (Form 2) Tablets and the new manufactured batch, 300 mg Ranitidine HCl (Form 1) Tablets.

c. Ranitidine HCl is very soluble in water, and products of Forms 1 and 2 are bioequivalent (Summary Basis of Approval: Ranitidine HCl, Zantac Tablets, Glaxo Inc., NDA 18-703, and Shen, J., Lee, D., and McKeag, R., Bioequivalence of Two Forms of Ranitidine, New Zealand Pharmacy, October 1995, P. 24-25).

d. The comparative dissolution testing conducted on both, Forms 1 and 2 of the 150 and 300 mg Ranitidine HCl Tablets, and 150 and 300 mg Zantac Tablets (Table 5).

e. Genpharm has manufactured and tested one lot of tablets using the new source. The comparative dissolution and stability testing meets the requirements in the "Office of Generic Drugs Policy and Procedure Guide #22-90, 4.D".

f. Formulations comparison of both, Forms 1 and 2 of the 150 and 300 mg Tablets (Table 6). Formulation of 300 mg Ranitidine HCl (Form 1) Tablets is the same as formulation of 300 mg Ranitidine HCl (Form 2) Tablets. Formulation of 150 mg Ranitidine HCl (Form 1) Tablets is the same as formulation of 150 mg Ranitidine HCl (Form 2) Tablets, except that Opadry II White [redacted] was used for Form 1, instead of Opadry II Orange [redacted], which was used for Form 2.

g. The bioequivalency of the test product, 150 mg Ranitidine HCl, Form 1 Tablets compared with 150 mg Zantac Tablets, Form 2 (current submission, September 27, 1996).

COMMENTS:

1. The 90% confidence intervals calculated using linear or ln-transformed parameters of the AUC(0-T), AUC(0-Inf), and C(Max) fall within the required range by the Division of Bioequivalence.

2. Samples from subject #16 were reassayed since the elimination profiles for both phases were found to be inconsistant. The reassayed values were reported. The 90% CIs (calculated by the reviewer) using ln-transformed parameters excluding this subject fall also within the required range by the Division of Bioequivalence.

3. Lots #100861 (test product) and #5ZPT009 (reference product) were used for both, the bioequivalence study and the dissolution testing. The test product batch size was [redacted] Tablets.

4. The values of C(Max), T(Max), and T(1/2) were similar for the test and reference products, and those reported in the Physicians' Desk Reference, 1996.

5. No error was detected in spot checking of the calculations, and statistical data analyses.

[redacted]

[redacted]

8. Twenty six (26) healthy male volunteers were enrolled in the study. Twenty-five (25) subjects completed the study. Subject #10 (sequence 2) did not return for phase II of the study.

9. The dissolution testing method was the same as the one reported in the USP 23, 1995.

DEFICIENCY: None.

RECOMMENDATIONS:

1. The fasting bioequivalence study submitted by Genpharm Inc. Pharmaceuticals on its Ranitidine HCl (Form 1), 150 mg, Tablets, Lot #100861 comparing it to Glaxo Pharmaceuticals, Zantac^{R}, 150 mg, Tablets, Lot #5ZPT009 has been found acceptable by the Division of Bioequivalence. The study demonstrates that Genpharm's Ranitidine HCl (Form 1), 150 mg, Tablets is bioequivalent to the reference product, Zantac, 150 mg, Tablets manufactured by Glaxo Pharmaceuticals.

2. The dissolution testing conducted by the Genpharm Inc. Pharmaceuticals on its Ranitidine HCl (Form 1), 150 mg, Tablets, Lot #100861, and Ranitidine Hcl (Form 1), 300 mg, Tablets, Lot #100862 has been found acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than [redacted] of the labeled amount of the drug in the dosage form is dissolved in 45 minute.

4. The firm's waiver request for the bioequivalence study requirements for its 300 mg Ranitidine HCl (Form 1) Tablets may be granted.

[redacted]

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE [redacted]
FT INITIALED RMHATRE [redacted] 4/8/97

Concur: [redacted] Date: 5/12/97

for Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

FNouravarsani/04-03-97/74023SDW.996

cc: ANDA #74-023 (original, duplicate), Nouravarsani, HFD-658, Drug File, Division File

Table 1

Mean (CV%) Serum Concentrations (ng/mL) of Ranitidine, N=25:

Time, hr	Test Product	Reference Product
0.00	0.00 (--)	0.00 (--)
0.33	58.96 (91)	59.34 (83)
0.67	212.57 (49)	222.34 (41)
1.00	278.32 (56)	283.96 (47)
1.33	286.24 (51)	286.83 (47)
1.67	303.96 (61)*	238.94 (31)**
2.00	338.76 (55)	287.84 (54)
2.50	337.32 (46)	331.60 (44)
3.00	335.52 (40)	354.16 (40)
3.50	328.96 (35)	335.72 (34)
4.00	298.40 (35)	319.76 (39)
5.00	230.12 (31)	257.32 (37)
6.00	168.56 (33)	186.05 (35)
8.00	104.50 (32)	112.15 (33)
10.00	60.11 (35)	66.46 (36)
12.00	34.42 (39)	37.31 (40)
16.00	10.32 (86)	12.45 (75)
20.00	1.08 (347)	2.21 (238)

* N = 23
** N = 22

Table 2:

Comparison of Mean (CV%) Ranitidine Pharmacokinetic Parameters, and 90% CI Obtained for 150 mg Tablets of the Test and Reference Products, N=25:

Parameters	Test	Reference	90% CI(ln-trans.)
AUC(0-T) hr*ng/mL	2172.0(32.7)	2278.2(28.4)	86.0 - 104.0
AUC(0-Inf) hr*ng/mL	2242.1(31.7)	2344.4(27.6)	86.0 - 104.0
C(Max) ng/mL	430.8 (38.3)	439.5 (32.8)	85.0 - 108.0
T(Max) hr	2.694 (37.9)	2.820 (40.6)	
K(Elm) 1/hr	0.261 (12.6)	0.259 (13.7)	
T(1/2) hr	2.70 (12.2)	2.728 (14.8)	

Table 3: AUC(0-T)/AUC(0-Inf) Percentage, N=25:

Subject	Test	Reference
01	[redacted]	
02		
03		
04		
05		
06		
07		
08		
09		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		
26		
Range%	92.0%-98.0%	93.0%-99.0%

Table 4: Ratio Analysis of the Parameters, N=25:

Subject	(Test/Reference) Percentage AUC(0-T)	AUC(0-Inf)	C(Max)
01	[redacted]		
02			
03			
04			
05			
06			
07			
08			
09			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
Mean%	98.1	98.4	101.1
CV%	26.2	26.1	34.0
Range%	54.0-147.1	53.9-148.9	42.7-182.8

Table 5: In Vitro Dissolution Testing

Drug (Generic Name): Ranitidine HCl
Dose Strength: 150 and 300 mg Tablets
ANDA #74023
Firm: Genpharm Inc. Pharmaceuticals
Submission Date: December 16, 1996

I. Conditions for Dissolution Testing:

USP XXII Basket ___ Paddle X RPM 50 No. Units Tested 12

Medium: Water at 37C Volume: 900 mL

Reference Drugs: Zantac, 150 and 300 mg Tablets, Glaxo Inc.

Assay Methodology: [redacted]

II. Results of In Vitro Dissolution Testing:

Sampling Times Min	Ranitidine Tablets Form 1 Lot #100861 150 mg			Zantac Tablets Lot # 5ZPT009 150 mg			Ranitidine Tablets Form 2 Lot # 100315 150 mg		
	Mean%	Range%	CV%	Mean%	Range%	CV%	Mean%	Range%	CV%
05	16.0	[redacted]	(48.4)	11.3	[redacted]	(16.5)	18.5	[redacted]	50.1)
10	44.7		(21.9)	35.4		(18.5)	48.7		(32.3)
15	65.6		(13.6)	54.6		(15.4)	80.4		(14.3)
20	88.7		(4.34)	72.4		(11.0)	96.0		(1.78)
30	96.9		(2.31)	92.1		(7.98)	97.4		(1.31)
45	98.0		(1.88)	99.4		(2.16)	97.4		(1.22)

Sampling Times Min	Ranitidine Tablets Form 1 Lot #100862 300 mg			Zantac Tablets Lot # 5ZPT001 300 mg			Ranitidine Tablets Form 2 Lot # 100316 300 mg		
	Mean%	Range%	CV%	Mean%	Range%	CV%	Mean%	Range%	CV%
05	35.0	[redacted]	31.6)	16.5	[redacted]	(44.5)	46.0	[redacted]	30.4)
10	75.8		10.0)	43.9		(25.1)	80.2		(10.4)
15	91.2		4.47)	67.3		(12.5)	93.6		(2.23)
20	96.1		1.63)	88.0		(3.09)	95.9		(1.57)
30	96.4		(1.46)	97.3		(2.26)	96.3		(1.08)
45	96.9		(1.35)	98.8		(1.18)	96.5		(1.18)

Table 6:

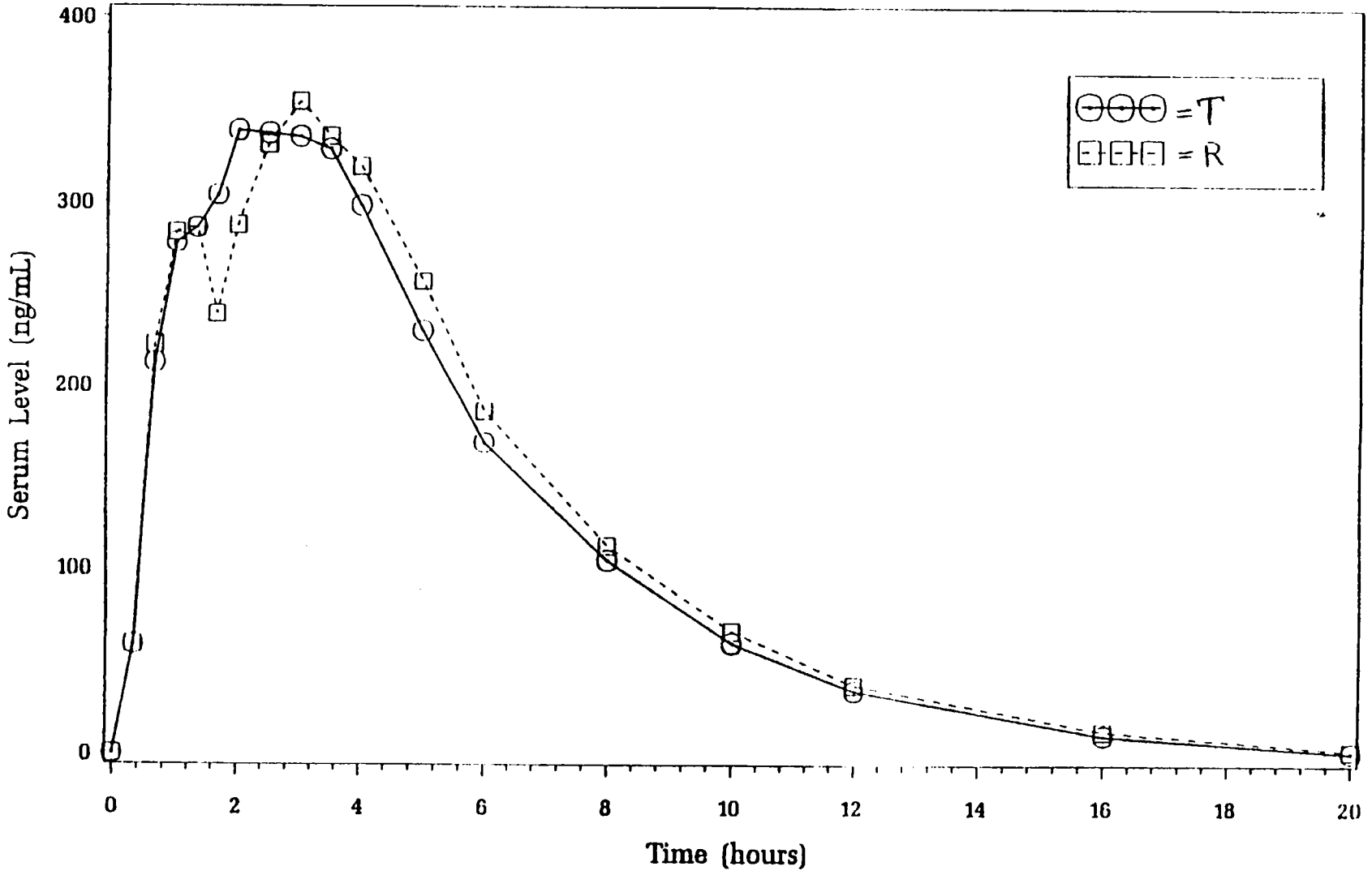
Formulation Comparisons of 300 and 150 mg Ranitidine HCl, Form 1 and Form 2, Tablets:

Ingredients	Form 1 300mg	Form 1 150mg	Form 2 300mg	Form 2 150 mg
Ranitidine HCl	336.00*	168.00*	336.00*	168.00*
Microcrystalline Cellulose, NF	[redacted]			
Croscarmellose Sodium, NF	[redacted]			
Magnesium Stearate NF	[redacted]			
[redacted] Orange 1	[redacted]			
[redacted] White 6	[redacted]			
Purified Water, USP	[redacted]			

* = 336 mg and 168 mg Ranitidine HCl are equivalent to 300 mg and 150 mg Ranitidine base, respectively.

Figure 1: Mean Ranitidine Serum Levels

n = 25



Ranitidine Hydrochloride
Tablets, USP, 150 mg
ANDA #74-023

MAY 2 [illegible] 1993

SPONSOR:
Genpharm Pharmaceutical Inc.
37 Advance Road
Etobicoke, Ontario, Canada M8Z 2S6

AGENT:
Eugene Pfiefer
King & Spalding
1730 Pennsylvania Avenue N.W.
Washington DC, 20006

Dear Mr. Pfiefer:

Reference is made to the *in vivo* bioequivalence study and dissolution data which you submitted on November 18, 1992 in support of your ranitidine hydrochloride tablets.

The material has been reviewed by the Division of Bioequivalence and we have the following comments:

DEFICIENCIES:

I. [redacted]

II. The batch size of the Test product used in the bioequivalence study and dissolution testing should be reported.

RECOMMENDATION:

The bioequivalence study submitted by Genpharm Inc. Pharmaceuticals on its ranitidine, 150 mg tablets, lot #T11-3-150 comparing it to Glaxo Pharmaceuticals, Zantac®, 150 mg Tablets lot #Z12350NP has been found incomplete by the Division of Bioequivalence for the Deficiencies #I & #II.

All responses and correspondence with regard to this letter should be sent to the Office of Generic Drugs, HFD-630.

Sincerely yours,

Ramakant M. Mhatre, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

cc: Date _____
HFD-632 Pollock/Random 6
HFD-650 (Mhatre, Greenberg, CST)
stm 05-19-93 (N74023.STD)
bio letter

APR 20 1993

Ranitidine Hydrochloride
Tablets, USP, 150 mg
ANDA #74-023
Reviewer: F. Nouravarsani
74023SD.N92

Genpharm Inc. Pharmaceuticals
Ontario, Canada
Submission Date:
November 18, 1992

Review of a Bioequivalence Study Amendment

INTRODUCTION:

Genpharm Inc. Pharmaceuticals had previously submitted a comparative bioequivalence study and dissolution testing conducted on its Test product, Ranitidine Hydrochloride Tablets, 150 mg, and Zantac^{R} Tablets, Ranitidine hydrochloride, 150 mg, manufactured by Glaxo Pharmaceuticals (NDA #18703-001) as the listed Reference product (submission letter dated March 12, 1992). The study was found to be incomplete. The deficiencies communicated to the firm by letter dated September 23, 1992, and the firm's responses are summarized as follows:

Deficiency #1:

[redacted]

Response to Deficiency #1:

[redacted]

Reviewer Comment:

[redacted]

[redacted]

The firm should be advised to calculate the 90% confidence intervals for the pharmacokinetic parameters of AUC(0-T), AUC(0-Inf), and C(Max) by including subjects #11 and #12, and excluding the replacement subjects #25 and #26.

Deficiency #2:

[redacted]

Response to Deficiency #2:

[redacted]

Reviewer Comment:

The firm's response is acceptable.

Deficiency #3:

[redacted]

Response to Deficiency #3:

[redacted]

Reviewer Comment:

The firm response is acceptable.

Deficiency #4:

Total of 67 samples were diluted 2 times or more. The original values of these samples should be reported.

Response to Deficiency #4:

Reviewer Comment:

The firm's response is satisfactory.

Deficiency #5:

The firm should report the batch size of the Test product.

Response to Deficiency #5: None

Deficiencies of the Current Submission:

II. The batch size of the Test product used in the bioequivalence study and dissolution testing should be reported.

RECOMMENDATION:

The bioequivalence study submitted by Genpharm Inc. Pharmaceuticals on its Ranitidine, 150 mg Tablets, lot #T11-3-150 comparing it to Glaxo Pharmaceuticals, Zantac^{R}, 150 mg Tablets lot #Z12350NP has been found incomplete by the Division of Bioequivalence for the Deficiencies #I & #II.

[redacted]

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE [redacted]

FNouravarsani/04-19-93/74023SD.N92

CC: ANDA #74-023 (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-344 (CViswanathan), HFD-658 (Mhatre, Nouravarsani), Drug File, Division File.

JUL 28 1992

Ranitidine Hydrochloride
Tablets, USP, 300 mg, Oral
ANDA #74-023
Reviewer: F. Nouravarsani
74023S.392

Genpharm Inc. Pharmaceuticals
Ontario, Canada
Submission Date:
March 12, 1992

Review of a Request for an Unacceptable Bioequivalence Study

Genpharm Inc. Pharmaceuticals had submitted an unacceptable bioequivalence study conducted under fasting conditions on its Test product, Ranitidine Hydrochloride Tablets, 300 mg comparing it with Zantac® Tablets, 300 mg manufactured by Glaxo Pharmaceuticals (submission date: February 04, 1991).

In the current submission the firm has responded to the deficiency letter of the Division of Bioequivalence dated February 05, 1992, and has requested the Division of Bioequivalence to reconsider the evaluation of the study and accept the study.

The study was unacceptable for the following deficiencies:

[redacted]

Response 1a:

[redacted]

The above response summarizes the acceptance criteria for the quality control samples, and does not change the fact that a significant number of standard curves and quality control samples were found unacceptable.

[redacted]

Response 1b:

[redacted]

The firm has clarified the base of acceptance of the quality control samples for its unacceptable study.

[redacted]

Response 1c:

[redacted]

Response 1d:

[redacted]

The firm corrected its previous report that only 2 standard samples deviated more than 15% from the nominal values.

[redacted]

Response 1e:

[redacted]

2. The summary of the pre - study assay validation to determine ranitidine in serum has not been submitted for review.

Response 2:

[redacted]

3. Samples with concentrations above quantifiable limit were diluted before reassaying. The original values of some of these samples were not reported.

Response 3:

[redacted]

[redacted]

4. The waiver request of bioequivalence study requirements for 150 mg Ranitidine Tablets was not granted, since the firm has not conducted an acceptable bioequivalence study on the higher strength of the Ranitidine Tablets, 300 mg. Furthermore, the comparative dissolution testing conducted on the 150 mg Ranitidine Tablets and 150 mg Zantac^{R} Tablets was unacceptable. The deviations between the means of the Test and Reference products were very high at all the time intervals except for the 30 - 44 minutes interval. The obtained coefficient of variation (CV) of higher than 5% for the last time interval was also unacceptable.

Response 4:

In response to the rejection of the waiver request for the 150 mg Ranitidine Tablets, the firm has submitted a bioequivalence study and comparative dissolution testing conducted on 150 mg tablets. The review of this submission (ANDA 74-023, submission date: March 12, 1992) is attached.

Comments:

1. The above responses by the contract lab. does not change the fact that a significant number of standard and quality control samples were found unacceptable, and 4 subjects were dropped out from the study because of the assay failure.

[redacted]

The firm should be advised for the future studies to submit the values of original, reassayed, and the reason(s) for reassaying the samples. The accepted values and the reason for that should also be reported.

Recommendation:

The firm's unacceptable bioequivalence study of Ranitidine HCl, 300 mg Tablets was reconsidered, and it was determined that the firm's responses to the deficiencies were not satisfactory. The firm should be informed of the Comments and the Recommendation.

[redacted]

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE [redacted] 7/28/92

Concur:_____ Date:_____
Shrikant V. Dighe, Ph.D.
Director
Division of Bioequivalence

FNouravarsani/07-23-92/74023S.392

CC: ANDA #74-023 Amendment, HFD-630, HFD-604 (Hare), HFC-130 (JAllen), HFD-658 (Mhatre, Nouravarsani), Drug File.

JUL 28 1992

Ranitidine Hydrochloride
Tablets, USP, 150 mg
ANDA #74-023
Reviewer: F. Nouravarsani
74023SD.392

Genpharm Inc. Pharmaceuticals
Ontario, Canada
Submission Date:
March 12, 1992

Review of a Bioequivalence Study and Dissolution Testing

INTRODUCTION:

Genpharm Inc. Pharmaceuticals, submitted a comparative bioequivalence study and dissolution testing conducted on its Test product, Ranitidine Hydrochloride Tablets, 150 mg, and Zantac^R Tablets, ranitidine hydrochloride, 150 mg, manufactured by Glaxo Pharmaceuticals (NDA #18703-001) as the listed Reference product.

Ranitidine hydrochloride, a histamine H_2-receptor antagonist inhibits daytime and nocturnal basal gastric acid secretions. It also inhibits the gastric acid secretion stimulated by meal, pentagastrin, and betazole. The oral absolute bioavailability of Zantac is 50% . Mean peak levels of ranitidine are 440 to 545 ng/mL observed at 2 to 3 hours following a 150 mg dose.

The administration of food or antacids does not show a significant effect on the absorption of Zantac. The elimination half-life is reported to be 2.5 to 3 hours.

OBJECTIVES:

1. Determine the bioequivalency of the Test product, Ranitidine Hydrochloride Tablets, 150 mg and the Reference product, Zantac^R Tablets, 150 mg, under Fasting conditions.

2. Compare the in-vitro dissolution testing conducted on the Test and Reference products.

BIOEQUIVALENCE STUDY:

Sponsor: Genpharm Inc. Pharmaceuticals. The firm has appointed Steven Wentworth, Ph.D. as the United States agent to Genpharm for this submission.

Manufacturer: Genpharm Inc. Pharmaceuticals

[redacted]

[redacted]

Study Design:

A single dose of each Test and Reference products were administered randomly to healthy volunteers in an open - label, two - way crossover study design (project No. 13733).

Treatments:

Treatment A (Test Product): A single dose of Ranitidine Hydrochloride Tablets, 150 mg, Lot #T11-3- 150.

Treatment B (Reference Product): A single dose of Zantac^{R}, Ranitidine Hydrochloride Tablets, 150 mg, Lot #Z12350NP, Expiration date: August 1993.

Clinical Study Dates:

Phase I: March 22-23, 1991
Phase II: March 29-30, 1991
Washout period: 7 days

Subjects:

Twenty six (26) healthy male volunteers were enrolled in the study. Subjects 25 and 26 participated as possible replacements. All 26 subjects completed the study. However, subjects #11 and #12 were dropped from the study due to problems with assay of their samples. Samples from subjects #25 and #26 were assayed to substitute them. Subjects number 3, 4, 7, 8, 11, 14, 15, 16, 17, 20, 21, 23, and 26 received treatment A for phase I study. The rest of the volunteers (1, 2, 5, 6, 9, 10, 12, 13, 18, 19, 22, 24, and 25) were dosed treatment A for phase II. Subjects #2, 3, 6, 7, 11, 15, 20, 22, and 23 were smokers. The subjects were selected based on their health history, clinical laboratory tests and physical examinations. The range of the subjects age, weight, and height are summarized as follows:

Age: 19 - 50 years
Weight: 140 - 210 pounds
Height: 65.5 - 80 inches

Housing, Food and Fluid Intake:

All volunteers were housed in the [redacted] from 9.5 hours prior to the dosing and during the blood sample collection periods. The subjects fasted overnight prior to the dosing and 5 hours following the dose administration. The dose was taken with 240 mL of tap water. The standard meals were served 5 hours after the dose.

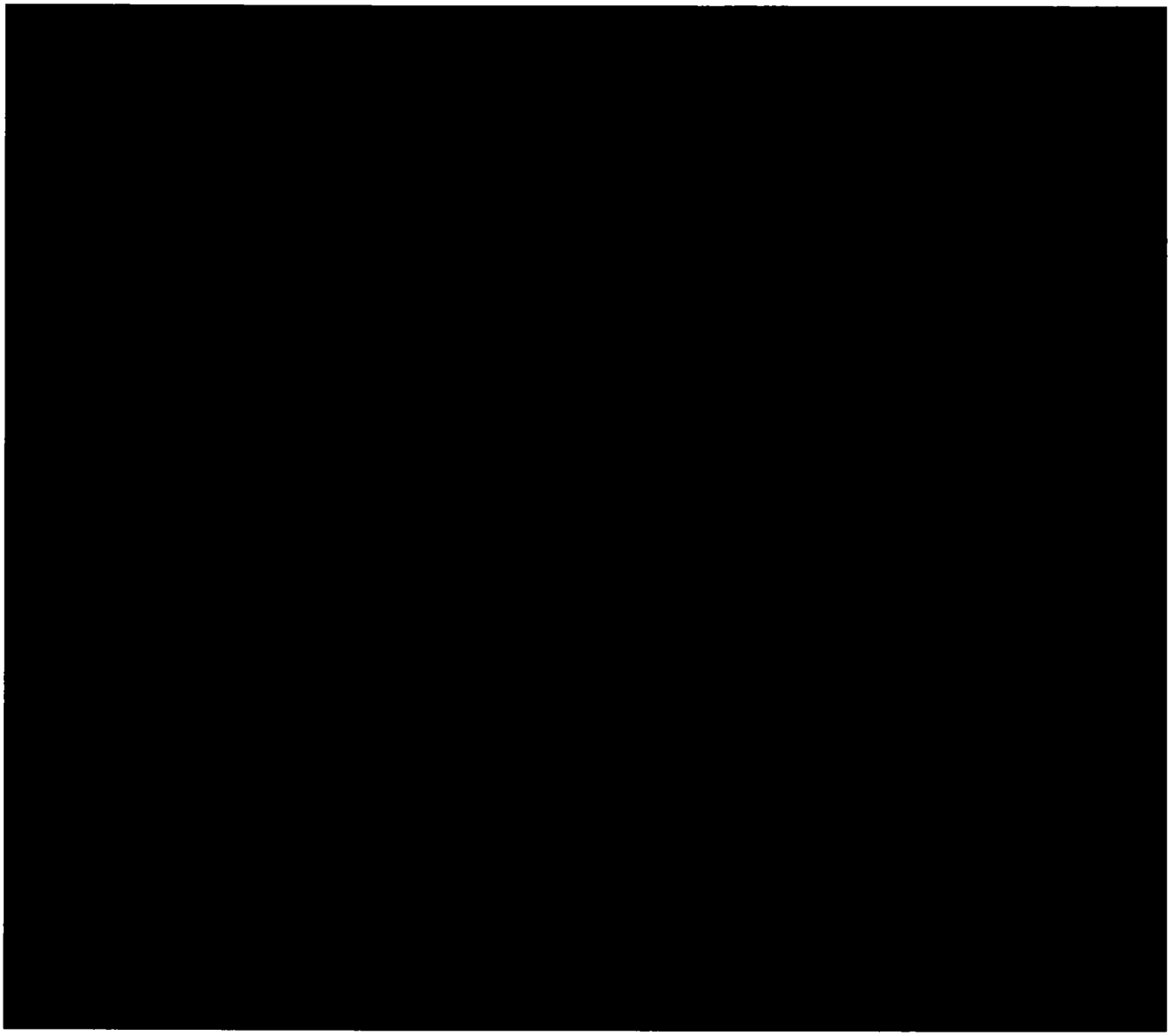
Blood Samples:

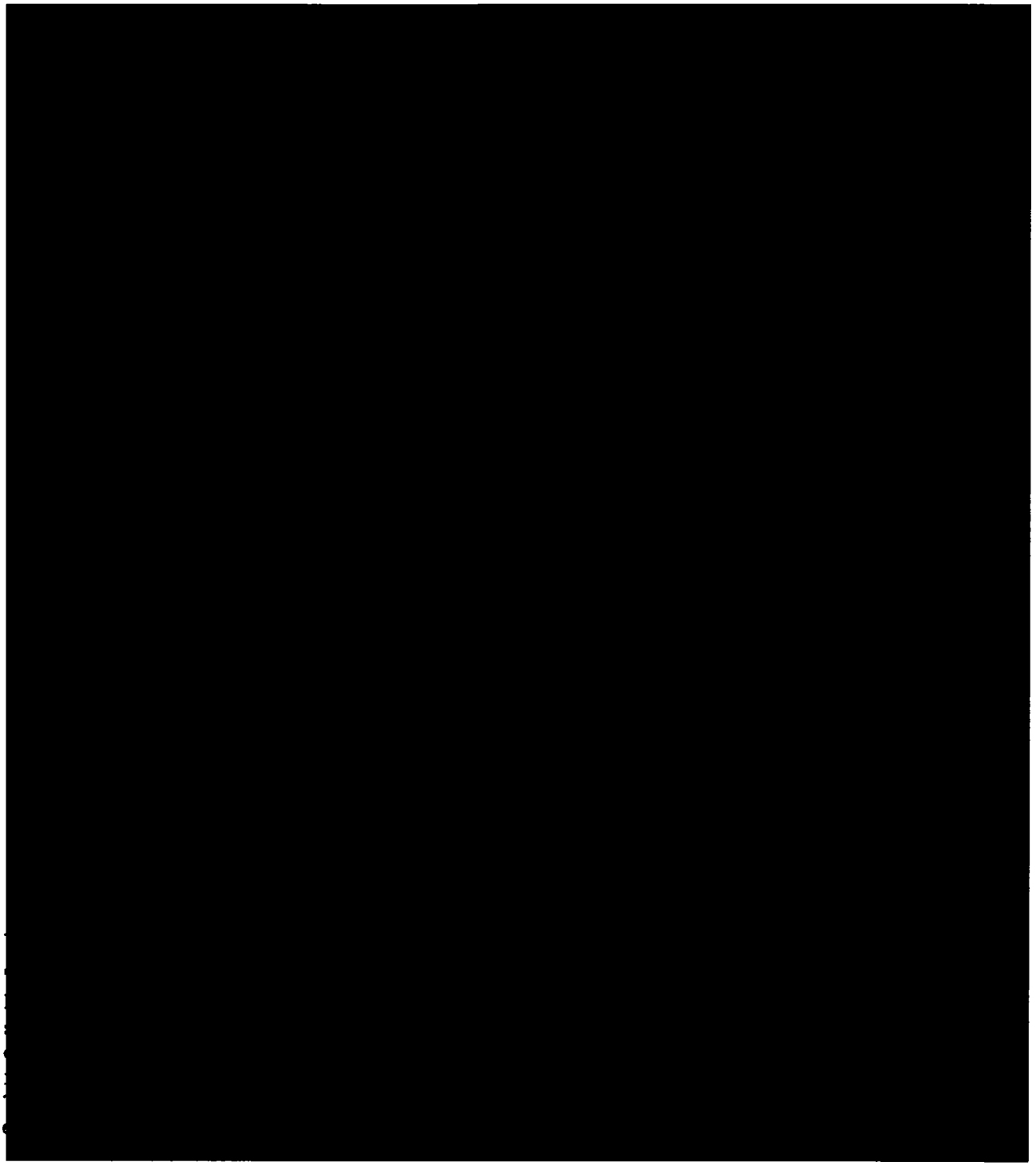
Blood samples of 10 mL were collected at predose, 0.33, 0.67, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 10.0, 12.0, and 16.0 hours after the dose.

Adverse Effects:

Subjects were monitored during the study for any adverse effects. Subjects number 14 and 15 (treatment B), and subject 21 (treatment A) reported mild headache.

Analytical Procedures:





Statistical Analysis:

The data were analyzed using SAS - GLM procedure. The two one sided test procedure (90% confidence intervals) was used to compare the least square means of pharmacokinetic parameters of AUC(0-TLQC), AUC(0-Inf), and C(Max) obtained from the Test and the Reference products.

Results:

The mean serum concentrations of ranitidine obtained for the Test and Reference products are summarized in Table 1. No statistically significant differences are observed between the products at each sampling time except for 2.5 hour using SAS - GLM procedure (p=0.05). Figure 1 shows plots of the mean plasma concentrations of ranitidine versus time for both, Test and Reference products. The mean of the pharmacokinetic parameters obtained for both, Test and Reference products are compared in Table 2.

The Test product AUC(0-TLQC) and AUC(0-Inf), 2476.0 hr*ng/mL and 2551.9 hr*ng/mL respectively are comparable with those obtained for the Reference product 2591.8 hr*ng/mL and 2650.4 hr*ng/mL respectively.

The mean C(Max) value of 457.9 ng/mL obtained for the Test product is also comparable with the mean C(Max) value of 496.5 ng/mL obtained for the Reference product.

The 90% confidence intervals (CI) for the parameters of AUC(0-TLQC), AUC(0-Inf), and C(Max) fall within the range required by the Division of Bioequivalence. No sequence, period, or treatment effects are observed for these parameters using SAS-GLM procedure.

Parameters	90% CI (linear)		90% CI (Ln)	
AUC(0-TLQC)	87.2	103.8	87.2	103.8
AUC(0-Inf)	88.0	104.5	88.1	104.6
C(Max)	82.2	102.3	83.3	103.4

IN - VITRO STUDIES:

Dissolution Testing:

Results of the dissolution testing conducted on 12 units of the same lots of the Test (#T11-3-150) and Reference (#Z12350NP) products used in the bioequivalence study are shown in Table 3. Over [redacted] (mean of 12 units) of the labeled amount of the ranitidine was dissolved in 45 minutes for the Test product. The dissolution of no units was less than Q - 15% . Mean of the dissolution of 12 units of the Reference product (Q = [redacted] is slightly less than [redacted] The dissolution of no units is less than Q - 15% for each product.

Assayed Potency:

Mean values of 99.5% and 99.3% of the labeled claim were obtained for ranitidine from assay of the Test and Reference products respectively.

COMMENTS:

1. Lots #T11-3-150 (Test product) and #Z12350NP (Reference product) were used for both, the bioequivalence study and the dissolution testing. The Test product batch size was not stated.

2. The dissolution testing conducted on 150 mg Ranitidine Tablets is acceptable.

3. The 90% confidence intervals calculated using linear or Ln transformed parameters of the AUC(0-TLQC), AUC(0-Inf), and C(Max) fall within the required range by the Division of Bioequivalence. However, subjects #11, and #12 were dropped from the statistical data analysis. Samples obtained from these subjects were analyzed twice on standard curves which were not acceptable, and there were not sufficient sample volumes available for reanalysis. Samples from subjects #25 and #26 were analyzed to replace volunteers #11 and #12.

4. Double peaks are observed for 20 out of 24 subjects for the Test product, and 21 out of 24 subjects for the Reference product. The peak with the higher value was reported as the C(Max). This secondary peak of the ranitidine has also been reported in the literature (J. Pharm. Sci., 78, #12, 1989, P 990).

5. No error was detected in spot checking of the calculations.

DEFICIENCIES:

[redacted]

4. Total of 67 samples were diluted 2 times or more. The original values of these samples should be reported.

5. The firm should report the batch size of the Test product.

RECOMMENDATIONS:

1. The bioequivalence study submitted by Genpharm Inc. Pharmaceuticals on its Ranitidine, 150 mg, Tablets, Lot # T11-3-150 comparing it to Glaxo Pharmaceuticals, Zantac^{R}, 150 mg, Tablets, Lot # Z12350NP has been found incomplete by the Division of Bioequivalence.

2. The dissolution testing conducted by the Genpharm Inc. Pharmaceuticals on its Ranitidine, 150 mg, Tablets, Lot # T11-3-150 is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP XXII apparatus II (paddle) at 50 rpm. The Test product should meet the following specifications:

Not less than [redacted] of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

The firm should be informed of the DEFICIENCIES #1-5 and the RECOMMENDATION #1.

[redacted]

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE [redacted] 7/28/92

Concur: [redacted] Date: 7/28/92
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Director
Division of Bioequivalence

FNouravarsani/07-23-92/74023SD.392

CC: ANDA #74-023 Original, HFD-630, HFD-604 (Hare), HFC-130 (JALLEN), HFD-658 (Mhatre, Nouravarsani), Drug File.

Table 1

Mean (CV%) serum Concentrations (ng/mL) of Ranitidine, N=24:

Time, hr	Test Product	Reference Product
0.00	000.0 (00.0)	000.0 (00.0)
0.33	64.4 (96.4)	72.0 (64.2)
0.67	205.8 (43.3)	224.8 (34.0)
1.00	288.7 (32.3)	286.6 (40.3)
1.50	327.5 (36.1)	336.0 (46.8)
2.00	328.3 (42.7)	360.7 (48.9)
2.50	343.5 (39.9)	412.3 (41.9)
3.00	370.4 (33.9)	411.1 (40.7)
3.50	358.6 (39.2)	402.1 (29.6)
4.00	347.1 (33.2)	352.0 (27.7)
6.00	218.8 (35.1)	214.6 (29.8)
8.00	117.9 (37.4)	122.9 (32.5)
10.00	78.1 (36.7)	71.5 (34.1)
12.00	38.3 (44.6)	36.1 (48.8)
16.00	14.5 (58.6)	15.5 (38.7)

Table 2

Comparison of the Mean (CV%) Pharmacokinetic Parameters for Ranitidine Obtained for the Test and Reference Products, N=24:

Parameters	Test Product	Reference Product
AUC(0-TLQC) hr*ng/mL	2476.0 (26.5)	2591.8 (24.0)
AUC(0-Inf) hr*ng/mL	2551.9 (26.4)	2650.4 (23.9)
C(Max) ng/mL	457.9 (28.3)	496.5 (31.7)
T(Max) hr	2.56 (42.6)	2.98 (21.8)
K(El) 1/hr	0.2663 (8.8)	0.2752 (10.7)
T(1/2) hr	2.62 (8.8)	2.55 (11.4)

Drug (Generic Name): Ranitidine HCl
Dose Strength: 150 mg Tablets
ANDA #74023
Firm: Genpharm Inc. Pharmaceuticals
Submission Date: March 12, 1992

Table 3 - In Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXII Basket ___ Paddle X RPM 50 No. Units Tested 12

Medium: Water at 37 ± 0.5 C Volume: 900 mL

Reference Drug: Zantac, 150 mg, Glaxo Inc.

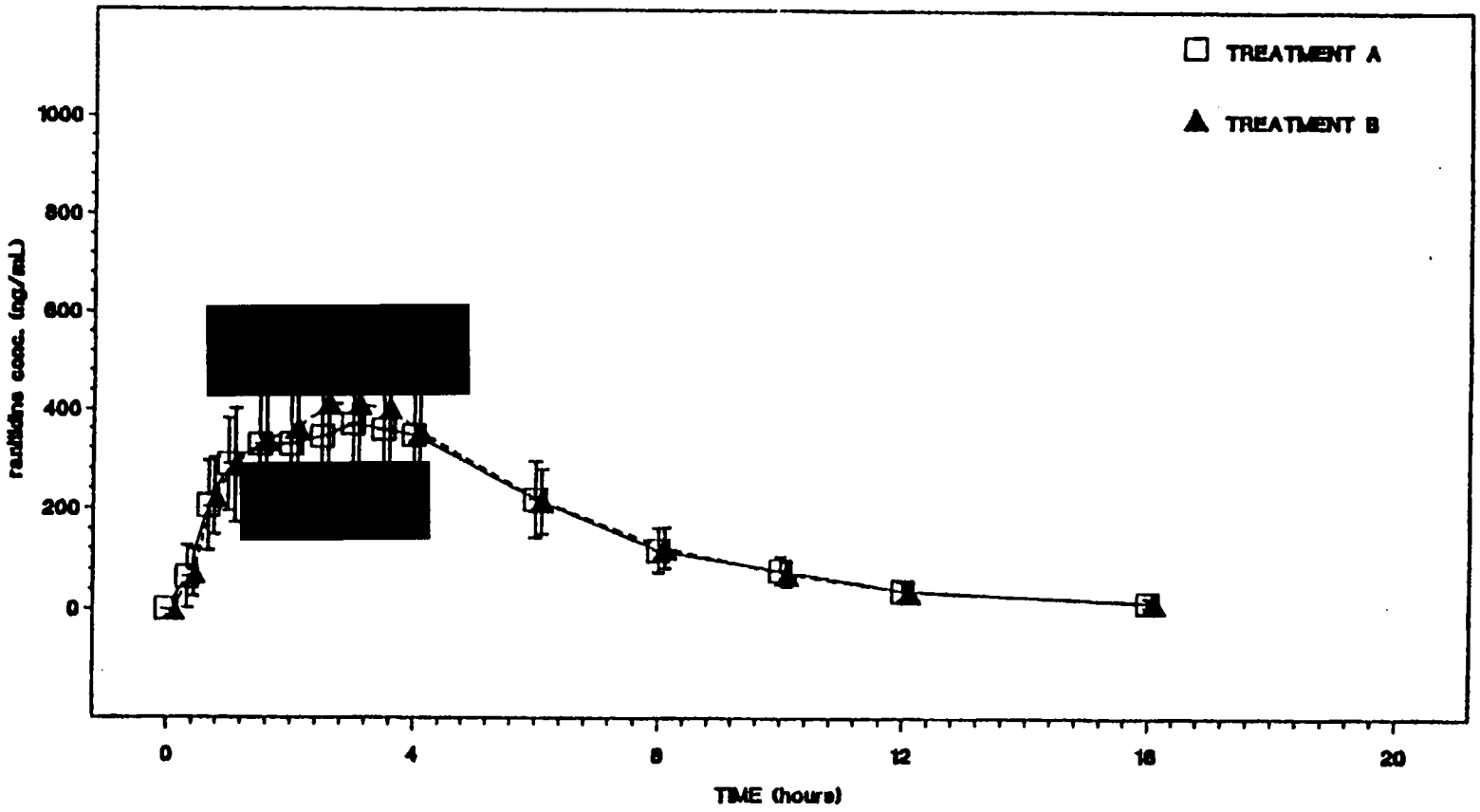
Assay Methodology: [redacted]

II. Results of In Vitro Dissolution Testing:

Sampling Times Min	Test Product Lot # T11-3-150 Strength (mg) 150 Mean%	Range%	(CV%)	Reference Product Lot # Z12350NP Strength (mg) 150 Mean%	Range%	(CV%)
9	25.6	[redacted]	(15.0)	22.6	[redacted]	(14.6)
21	55.2		(11.0)	52.0		(10.6)
30	79.4		(10.4)	69.0		(9.48)
45	88.3		(3.48)	79.7		(7.08)

TREAT A = ranitidine tablets, 150 mg
TREAT B = Zantac(R) tablets, 150 mg
ranitidine in serum

FIGURE 1
MEAN (S.D.) OF ALL VOLUNTEERS



LINEAR SCALE
TREATMENT B HAS BEEN OFFSET 0.1 HOURS TO FACILITATE VIEWING